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# THYROID AND THYMUS

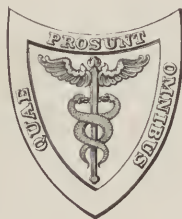
BY

✓  
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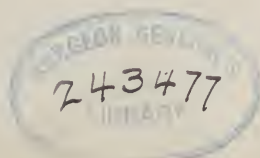
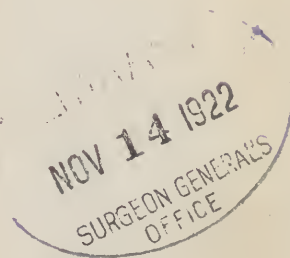
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TO  
DR. CHARLES H. MAYO  
FATHER OF AMERICAN GOITER SURGERY  
THIS BOOK  
IS RESPECTFULLY DEDICATED





## PREFACE TO THE SECOND EDITION.

---

THE kind reception accorded the first edition of "Thyroid and Thymus," and the pressing demands from a great many professional friends urging me to prepare a second edition, are responsible for the appearance of this new book. Almost all of the first issue has been revised and a great many chapters have been rewritten. To the extent of my ability, I have tried to take into consideration the helpful, constructive criticism offered at the time of the appearance of the first edition. An exhaustive bibliography has been added.

It is with pleasure and pride that I acknowledge the invaluable assistance of my dear wife in writing the chapter on the Etiology of Simple Goiter.

The success of the first edition is largely due to the artistic and high-class manner in which the book was handled by the publishers, Lea & Febiger, of Philadelphia. To them go my hearty thanks and appreciation.

Again, I wish to thank the artist, Marcel Guelin, for the new drawings he has contributed to this edition.

Miss Mary Scully, my competent and faithful secretary, is again entitled to a great deal of credit for the work done.

Prof. and Mrs. J. Philip Schneider, of Wittenberg College, Springfield, Ohio, have earned my gratitude by helping me see this book through the press.

Finally, I wish to acknowledge the splendid help received from the Journal *Endocrinology* in reviewing the literature, especially that of the Thymus. In some instances, I borrowed some of the reviews almost verbatim.

A. C.

COLUMBUS, OHIO.  
AUGUST, 1922.





## PREFACE TO THE FIRST EDITION.

---

THE following pages are the results of seventeen years' experience in the field of goiter pathology and surgery in Switzerland and in this country. When first assistant in the pathological laboratory of Prof. Henry Stilling, in Lausanne, Switzerland, I felt a marked attraction toward the goiter problem. Since then that interest has been steadily growing keener. It is not only of the utmost interest medically and surgically, but is also one of the most baffling problems so far as the etiology is concerned, and, furthermore, is of tremendous importance sociologically. The enormous loss to a community, to a state, to a country caused by the goiter pathology, be it hypothyroidism, hyperthyroidism, or cretinism, can scarcely be estimated. Consequently any effort to understand, to explain, or to combat that ailment should be welcome. It was with this end in view that I started to write this book. Some may find my statements somewhat dogmatic at times, and my conclusions perhaps a little sanguine. I feel, however, that in the study of the problems of internal secretion, always tantalizing and interesting, accessibility to ideas is the one prerequisite to success for those who wish to gain achievement in the study, and so long as we have not acquired the whole truth, opinions are of value provided they are substantiated by facts.

In addition to the years of personal experience in the study of the thyroid and thymus glands, I have gathered all that I considered of value from the enormous amount of French, Italian, German, and English literature on the subject, and I have endeavored, in my recital of sources and authorities, to give credit where credit is due.

It is my pleasant duty to express my profound gratitude and respect to the memory of my master, Henry Stilling, Professor of Pathology at the University of Lausanne, Switzerland. To him I owe much encouragement and self-confidence.

I have hoped that my great master, Professor Theodore Kocher, of Berne, Switzerland, would live to see this work in which he was greatly interested. Unfortunately, it was not to be. I owe so much to his inspiration and example that his memory will always be cherished by me.

It is with pleasure and pride that I acknowledge the invaluable

assistance of my dear wife in writing the chapter on the Etiology of Simple Goiter.

I wish to thank, also, Marcel Guelin, who formerly lived in Moscow, Russia, but is now "somewhere in Siberia." His anatomical drawings are the most beautiful and artistic I have ever seen. The difficulty of getting these plates to America (several sets were lost on the way) was a bit of exasperation that was an expected, though unwelcome, outcome of the disturbed conditions due to the Great War. If the work merits success, my friend Guelin must be entitled to a share of the credit.

To J. Philip Schneider, Ph.D., Professor of English, Wittenberg College, Springfield, Ohio, and to his wife, Clara Serviss Schneider, go hearty thanks for help in proofreading, in seeing the work through the press, and for the index.

Finally, I wish to acknowledge the assistance I have received from my secretary, Miss Mary Scully, whose untiring efforts have been of great value.

To those of my masters who are still alive to receive this contribution, I send greetings and offer heartfelt thanks for encouragement and inspiration. May they feel that what of ambition was aroused by their efforts was not aroused in vain.

I cannot close the chapter of my debts without mentioning Dr. J. F. Baldwin, surgeon at Grant Hospital, Columbus, Ohio, and without thanking him heartily for his cordial support and encouragement.

A. C.

COLUMBUS, OHIO.

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# DISEASES OF THYROID AND THYMUS.

## CHAPTER I.

### ANATOMY AND EMBRYOLOGY.

#### ANATOMY.

THE thyroid gland is an unpaired gland of reddish color. It lies upon the lateral surface of the thyroid and cricoid cartilages and upon the anterolateral surface of the upper end of the trachea, which it surrounds in a more or less horseshoe-like manner.

The thyroid gland consists of two *lobes* united by a narrow transverse portion, the *isthmus*. The lobes are conical in shape and measure about 2 inches in length,  $1\frac{1}{4}$  inches in width and  $\frac{3}{4}$  inch in thickness. The gland *in toto* weighs about an ounce. It must be well understood that these figures may vary. There are countries where the general average weight may be higher than the one just given, and yet the gland will still be normal.

It is customary to call the upper portion of a lobe *upper pole* and the lower portion *lower pole*, while the portion of the gland between the upper and lower poles may be called the *body* of the gland. Inwardly, each lobe comes in contact with the trachea, esophagus, thyroid and cricoid cartilages, the inferior laryngeal nerve, the inferior constrictor of the pharynx and the posterior part of the cricothyroid muscle. Its posterior surface is in relation with the carotid sheath containing the common carotid, the internal jugular vein and the vagus nerve; it is, furthermore, in relation with the inferior thyroid artery, with the parathyroids and also with the prevertebral fascia and muscles. The anterolateral surface is covered by the sternothyroid, the sternohyoid and the omohyoid muscles; the sternocleidomastoid muscles overlap the outer border of the gland.

The *isthmus* is situated in front of the trachea and covers its second, third and sometimes its fourth ring. It varies in size and width. Usually, it measures about  $\frac{1}{2}$  inch in breadth and the same in depth. It may even cover the cricoid cartilage, or at least part of it. In such cases superior tracheotomy presents some difficulties. The isthmus may be absent altogether (Fig. 1), or may be entirely separated from both lobes, thus forming a lobe by itself.

From the isthmus, or from the adjacent part of either lobe, a narrow strip of glandular tissue is often seen passing in front of the thyroid cartilage upward toward the body of the hyoid bone, to which it may or

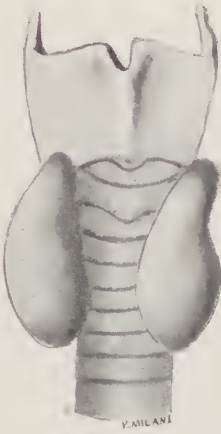


FIG. 1.—Thyroid without isthmus and without pyramidal process.

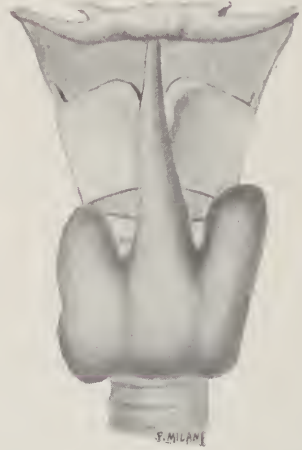


FIG. 2.—Thyroid with one pyramidal process.

may not be attached. The process is called the *pyramidal process* (Fig. 2). It is not constant and is found oftener on the left side than on the right. In rare cases the pyramidal process may be double (Fig. 3).



FIG. 3.—Thyroid with two pyramidal processes.



FIG. 4.—Thyroid gland whose isthmus does not join the two lobes.

It has the same structure as the thyroid gland. The pyramidal process represents the vestiges of the thyroglossus duct (Fig. 2).

The thyroid gland is in close connection with the trachea and with the larynx by interwoven connective tissue. It has special attachment

with the cricoid cartilage through bands of fibrous tissue extending from the isthmus and lateral lobes to the cricoid cartilage. These bands are known as the *suspensory ligaments* of the thyroid. It is on account of such relation that the latter organ follows the movements of the larynx during deglutition.

One lobe or even the entire thyroid gland may be wholly absent, but this is very rare indeed. I have recently found at operation a case where the left lobe was absent. In its place there was a little bit of a soft, yellowish fatty deposit.

*Accessory thyroids* are frequently found in the neck. They are more common in the neighborhood of the hyoid bone, but they may be found below the thyroid gland as far down as the arch of the aorta and the bifurcation of the trachea. They have the same histological structure as the thyroid gland itself; they may contain colloid or may show embryonical structure. Goiter or tumors of any kind can develop from them.

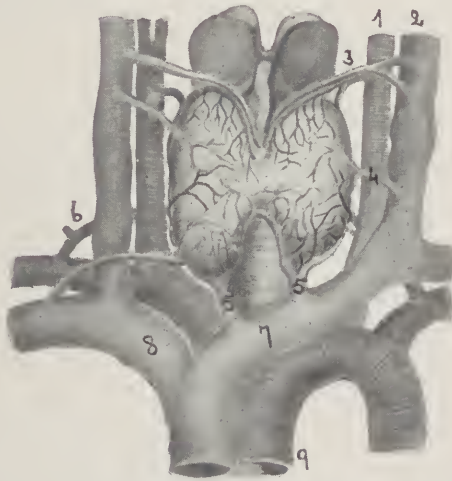


FIG. 5.—1, common carotid; 2, internal jugular vein; 3, superior thyroid artery and vein. Normally the artery originates a little higher up from the external carotid and not from the common carotid, as wrongly shown by the picture; 4, middle vein; 5, imæ veins; 6, inferior thyroid artery; 7 and 8, right and left innominate veins; 9, aorta.

**Blood Supply.**—The thyroid gland receives its blood supply from three arteries, the superior, the inferior and the ima artery (Fig. 5). The *superior thyroid artery* is the first branch of the external carotid. It runs in a curve forward and downward to the upper pole and gives off a branch for the hyoid bone, one for the sternocleidomastoid muscle, one for the larynx (the superior laryngeal artery, which perforates the thyrohyoid membrane) and one branch known as the cricothyroid artery, passing in front of the cricothyroid ligament just above the

isthmus. The artery finally splits into two terminal branches in the upper pole of the thyroid gland, the anterior and posterior branches.

The *inferior thyroid artery* arises from the thyrocervical trunk given off by the subclavian artery. It runs in front of the scalenus anticus muscle, at first upward, then bends inwardly, passing behind the carotid sheath, and terminates in the posterior surface of the thyroid gland.

The *ima artery* comes off directly from the arch of the aorta or from the innominate artery and terminates in the isthmus. It is not constant.

Anna Begoune has demonstrated that each artery supplies a territory of its own; the superior thyroid artery supplies the superior half of the lobe; the inferior thyroid artery supplies the inferior half of the lobe. This is of course very schematic and not literally true, as both territories exchange numerous anastomoses, which in time may grow into an important collateral circulation. If the four arteries are injected, not only the whole thyroid gland, but also the adjoining organs, as the trachea and the esophagus, will become injected at the same time. This is an important fact, as it shows that after ligation of all the thyroid arteries the gland may still receive some blood from its collateral circulation.

The *veins* of the thyroid gland show considerable variation. They form a rich plexus upon and beneath the capsule of the gland. The *superior thyroid vein* terminates generally in the thyro-linguo-facial trunk formed by the junction of the thyroid, lingual and facial veins. This trunk empties into the internal jugular vein. Often, however, the superior thyroid vein empties directly into the internal jugular vein. The superior thyroid vein is usually a single vessel, constituting a short, thick, venous trunk which passes transversely into the wall of the internal jugular vein. This anatomical relationship to the internal jugular vein must be borne in mind when ligating the upper pole, because if ligation of this vessel is not made carefully, profuse postoperative hemorrhage may follow. The *inferior thyroid vein* empties into the internal jugular vein. Not infrequently, as shown by Kocher, there is a *middle vein* which emerges from the side of the gland, passes transversely outward and empties into the internal jugular vein. The middle thyroid vein is short in length and may be easily overlooked when delivering the goiter. Here, too, injury to the vein may lead one to believe that the internal jugular has been damaged. From the lower border of the isthmus and both poles there is a plexus of two, three or more veins which go directly downward and empty into the innominate vein of both sides. They are known as the *imæ veins* (Fig. 5).

The thyroid veins have no valves.

These numerous bloodvessels, be they arterial or venous, pass to and fro, penetrate the gland and break into smaller branches. They



ultimately form a capillary network around each follicle and come in close contact with each cell.

The blood supply of the thyroid gland is very extensive, and in proportion to its size the circulation here is more extensive than in the brain. This abundant circulation shows that the function of the thyroid gland must be an important one.

**Lymphatics.**—Forming a network around each vesicle the *small lymphatics* resolve themselves into larger collecting trunks which empty either into the *prelaryngeal* group of lymph nodes located in front of the cricothyroid membrane, or into the *cervical* group all along the common carotid, or into the *pretracheal* group below the isthmus. Some of these deeper trunks empty into the lymph nodes along the posterolateral surface of the pharynx and esophagus.

The nerve supply comes from the sympathetic (median and inferior cervical ganglia) and from the vagus nerve (superior laryngeal branch). The inferior laryngeal nerve comes in close contact with the gland but does not supply it. The capsule of the thyroid contains sensory nerves.

## HISTOLOGY.

The thyroid gland has no excretory canal; it belongs to the group of glands of internal secretion. Although this is true, we must, however, admit that the secretion of the thyroid still affects the *external* type, since the products of cellular secretion empty into the alveoli under the form of colloid and are only later absorbed into the general circulation. We have, consequently, two distinct processes: one of secretion and the other of absorption.

The thyroid gland is composed of connective tissue and epithelium.

The connective tissue forms a capsule which surrounds the entire gland and projects inward, prolongations dividing the gland into lobules. These lobules contain round, tubular, sacculated, branching or prismatic vesicles or follicles, each one separated by more slender septa. In this stroma, be it interlobular or interfollicular, elastic fibers, nerves, blood and lymphatic vessels are found. The normal size of the alveoli varies from 50 to 300  $\mu$ . It is not quite uncommon to find in the parenchyma small foci of lymphoid tissue.

The epithelium is cuboidal or cylindrical and is arranged in one layer all around the wall of the follicle. The follicle in the thyroid gland has no *membrana propria*. Wegelin, however, has shown that a *membrana propria* exists in *goiter*, especially in cases in which hyalin degeneration is present. Each cell is provided with a single oval-shaped or round nucleus which contains a thin chromatin network with one or

more chromatin corpuscles. The diameter of each nucleus is generally from 5 to 6  $\mu$ . Acidophiles, granulations and fat are found in the cells.

Two types of cells are usually described in the thyroid vesicles: the "chief cells," far more numerous, clear and finely granular, and the "colloid cells," more opaque and more granular. Differences, however, between these two varieties are not sufficient to warrant differentiating them into two distinct types of cells. The colloid cells seem to be merely chief cells loaded with colloid material which has not yet been excreted into the alveolar lumen. For the majority of the thyroid cells the secretion affects the *merocrine type*. This means that a part only of the cell is used by the secreting process. Once elaborated the secretion is evacuated into the alveolar lumen by the breaking open of the nuclear membrane; then the cells regenerate and become "chief cells," ready to start over the secreting cycle. In numbers of other instances, however, the secretion affects the *holocrine type*. In these cases the whole cell is used for colloid production. Nothing remains afterward; the whole cell is destroyed.

Beside the alveolar epithelium there are more or less constantly found non-differentiated cells scattered without any apparent design throughout the interalveolar spaces. They are regarded as embryonic cells and apparently do not differ physiologically from the alveolar cells. For further details see Chapter on "Diffuse Adenomatosis."

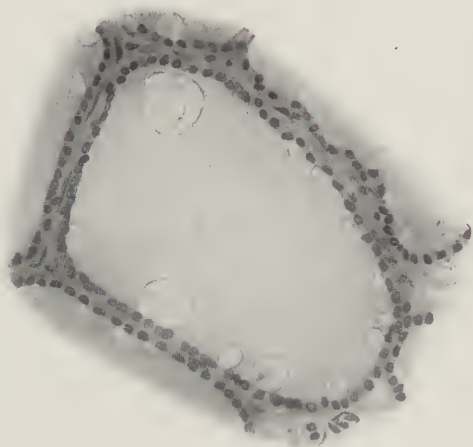


FIG. 6.—Colloid with its vacuoles.  $\times 350$ .

**Colloid.**—Some follicles are without lumen. The majority, however, contain *colloid substance*. Colloid may be fluid or thick. This difference in consistency is due to the difference in concentration of the albuminous substances. When filled with thick colloid the follicle



seems to be distended, but when it contains fluid colloid the follicle does not seem to be under tension.

The staining power of colloid is exceedingly variable. In the same microscopic field it is not rare to find alveoli in which the colloid did not stain at all and others which took the staining in the most intense manner. We may say, in a general way, that the thicker the colloid the more it will stain, although this is not always true, as solid lumps of colloid are not so rarely seen in which the staining has scarcely taken.

The thick or solid colloid looks homogeneous and must be regarded as a product which does not absorb as readily as thin colloid. It is quite common to find *vacuoles* in the colloid (Fig. 6). These vacuoles are often artefacts due to retraction of the colloid substance when it undergoes coagulation. These vacuoles are then located at the periphery of the coagulum and remain in connection with the walls of the follicle through very thin trabecules. Oftentimes, however, they are due to the presence of fat and mucine in the colloid. They are then more or less in the center of the colloid.

The colloid most generally enters the general circulation through the lymphatic spaces and vessels surrounding each follicle. These lymphatics often contain a substance with atypical staining qualities similar to the ones of colloid. That this substance is identical with the colloid is not as yet an absolute, demonstrated fact.

The amount of colloid found in a gland is by no means a true index of the functional activity of the thyroid. In the newborn and in Graves's disease the amount of colloid found is scant. The same is true in acute infectious diseases; there the colloid is diminished in direct proportion to the severity of the disease. Nobody, I presume, will contend that in these conditions the functional activity of the gland is diminished. Everything seems to disprove it; the experimental as well as the microscopic findings, and especially the increased blood supply. On the other hand the colloid is increased in conditions in which we know the functional activity of the gland is diminished, as in colloid goiter and hypothyroidism. Why such apparent discrepancies? Because, besides "secretion" there is another phenomenon just as important, and that is "absorption." The amount of colloid found in a gland depends upon these two processes, and the physiological activity of the thyroid depends largely upon the equilibrium between them. For instance, we may find very little or no colloid in an extremely active gland, because there is at the same time a rapid absorption of the thyroid products going on. On the other hand the quantity of colloid may be found materially increased in cases in which secretion and absorption are diminished. In these two instances we would draw false conclusions as to the functional activity of the gland if we should judge

it only by the amount of colloid found. One thing, however, seems to be certain: the amount of colloid, and especially its consistency, seems to be in direct relation with the increased vascularization. This is not only true in Graves's disease, in acute infectious processes, and in the thyroids of newborn babies, but has also been shown experimentally. With increased blood supply the colloid loses its thickness and becomes readily absorbable.

**Desquamation.**—Normally a few cells may decay, lose their connection with the alveolar walls and fall into the lumen of the alveoli, where they will gradually disintegrate and be eliminated. These desquamated cells are replaced by new ones. In pathological processes, especially in severe thyrotoxicosis, desquamation may be very marked. As a rule, it is always accompanied with thinning or absence of the colloid. It is always of severe prognosis.

### EMBRYOLOGY.

Marine says: "Ancestrally the thyroid exists in the chordates in two forms—as an elaborate ventral midline pharyngeal glandular groove, the so-called 'endostyle' in all the lower chordates—tunicates, amphioxus and ammocetes (larval lampreys) and as the familiar ductless thyroid in all higher chordates—adult lampreys, fish, mammals, amphibians, birds and reptiles. Fortunately, the animal (lamprey) in which the transition from endostyle to thyroid can be followed still exists, otherwise this extraordinary metamorphosis could not have been established."

The thyroid is primarily a dependency of the esophagus (tunicians ammocetes) and in its endostyle form is a digestive gland of great importance through its external secretion. In its ductless form it is only the atrophic remnant of its ancestor, which, while it has suffered a corresponding distortion of function, still profoundly influences the animal's nutrition through the effects of its internal secretion.

The thyroid gland is found in the anterior portion of the neck of every vertebrate animal. It is absent in the amphioxus. It originates from an unpaired formation, the *tuberculum impar* of His, which is formed in the middle line by an evagination of the epithelium of the anterior pharyngeal wall, at the level of the second branchial arch, in or slightly anterior to the first aortic arch. For a long time it was thought that the thyroid gland had a double origin and was formed by the fusion of the median and lateral thyroids, originating from the median and lateral "anlagen." However, Müller, His, Verdun and Tournoux, after careful investigations, have come to the conclusion that the thyroid originated only from a single median evagination taking place in the anterior wall of the pharynx, between the three

divisions of the tongue, from which place it descends into the neck to its resting-place astride the upper portion of the trachea.

On a frontal and vertical cut the human embryo, two weeks old, shows laterally of the cephalic extremity a series of branchial arches separated by branchial grooves. In the human embryo of six months five branchial grooves are present, the fourth being divided into two. Between the second, third, fourth and fifth branchial arches on both sides; and between the inferior maxillary and the base of the heart, there is a triangular space which is called the *mesobranial field of His* (Fig. 7). From this field will derive the thyroglossus duct and the thyroid gland. Laterally of the mesobranial field of His are found *branchial arches* and *branchial grooves*, which altogether form the *branchial apparatus*. Branchial arches and branchial grooves are separated, one from the other, by a thin wall of tissue covered inside with *endoderm* and outside with *ectoderm*. These branchial and mesobranial elements give rise to very different and very important organs and to very well-differentiated embryonic residues from which thyroid tumors may derive. Therefore, from an embryological point of view, it seems logical to divide the tumors of the thyroid into *tumors of mesobranial origin* and *tumors of branchial origin*.

**Thyroglossal Duct.**—In the mesobranial field, just in front of the second groove, a median invagination of the walls of the pharynx appears, forming a depression which becomes deeper and deeper, and finally forms the *thyroglossal duct*. At its lower end this duct bifurcates, forming two terminal buds which proliferate into a glandular organ (Fig. 7) which later on will be the thyroid gland.

In the middle of the second month of intra-uterine life the thyroglossal duct divides into two portions, the superior and the inferior. The superior portion, called the *lingual portion*, extends from the foramen cecum of the tongue to the hyoid bone; the lower portion, or *thyroid portion*, extends from the hyoid bone to the isthmus of the thyroid gland.

This division of the thyroglossal duct into the lingual and thyroid portions is produced by the hyoid bone, which, at the end of the fifth week, is represented by a cartilaginous mass interposed between the two segments of the thyroglossal duct. Sometimes this interposition does not take place, and in that case the thyroglossal duct forms a continuous canal extending from the foramen cecum of the tongue to the thyroid gland. The tract travels from the foramen cecum through the posterior part of the tongue, following the lingual raphé, passes either in front, through or behind the hyoid bone, intimately connected with the periosteum and the thyrohyoid membrane and travels along the anterior surface of the trachea to the isthmus.

Ordinarily, the thyroglossal duct bifurcates in front of the larynx, forming the isthmus, the lobes being formed by the two terminal buds. However, the bifurcation of the thyroglossal duct may take place higher up, as far up as the foramen cecum; in that case we shall have two pyramidal processes, one on each side, or we may have two lobes with two pyramidal processes, but no isthmus at all (Figs. 1-4). In the *echidna* the lateral thyroid masses do not unite with the median thyroid.

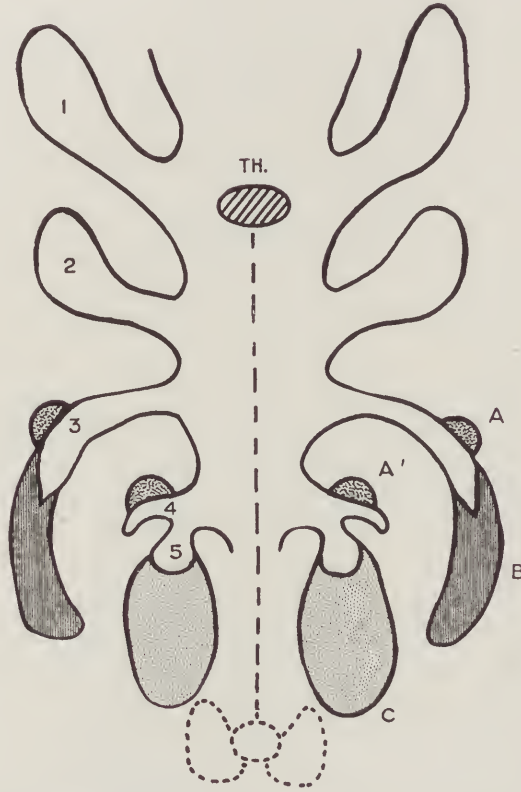


FIG. 7.—1, first branchial groove; 2, second branchial groove; 3, third branchial groove; 4, fourth branchial groove; 5, fifth branchial groove; *A*, thymic portion of the parathyroid; *A'*, thyroid portion of the parathyroid; *B*, thymus; *C*, postbranchial body; *TH*, thyroid.

The thyroglossal duct has a constant and specific structure. It is lined with one layer of cylindrical epithelium often ciliated. Very rarely is this duct lined with pavementous epithelium. The terminal portion of the thyroglossus, which constitutes later on the thyroid gland, has at first the same cylindrical structure, so that at the end of the fifth or sixth embryonic month the thyroid is formed by alveoli lined with one single layer of cylindrical epithelium; their lumen is



very small and does not contain colloid; protoplasm is clear, and has no vacuoles; nuclei are compact and the chromatin forms a stain instead of a network.

Later on this epithelium loses its cylindrical character, and at the end of the seventh month the structure of the thyroid gland has changed considerably; an intense cellular desquamation has taken place and fills the lumen of the alveoli, so that toward the end of the intra-uterine life the thyroid is composed of a uniform, non-differentiated mass of cells (Fig. 8), pressed one against the other and containing a few capillary



FIG. 8.—Congenital goiter. Simple parenchymatous goiter formed by a cellular mass not yet differentiated into adult alveoli.  $\times 58$ .

vessels. The nuclei are large, swollen, clear; no colloid is present. The cause of the desquamation is yet unexplained. A few weeks after birth, however, regeneration of the thyroid takes place; the epithelium shapes itself into epithelial cords which undergo a process of direct division, thus forming new alveoli in which the epithelium becomes cubic or flat.

Consequently, it may be said that the thyroid passes through three different stages:

1. The *embryonic* or *thyroglossal stage* formed by cylindrical epithelium.

2. The *fetal stage* formed by a non-differentiated cellular mass.
3. The *adult* or *vesicular stage*.

The embryonic and fetal types may leave persistent inclusions in the thyroid. Wölfler has demonstrated that these inclusions of fetal parenchyma are not seldom found in the thyroid, and that they may result in the production of a tumor known as the fetal adenoma.

After the thyroglossal duct has formed the thyroid gland with its lobes and isthmus, it gradually becomes atrophied and forms a fibrous cord called by His the *thyroglossus tractus*, which extends from the foramen cecum of the tongue to the pyramidal process. In the normal human embryo the duct begins to atrophy during the fifth week of the intra-uterine life and is closed usually by the eighth week leaving behind a depression in the tongue, known as the foramen cecum. Exceptionally, this canal may remain permeable in all its course from the tongue to the thyroid. When this is the case the thyroglossal duct leaves over its entire course islands of thyroid tissue, at the cost of which, later on, *accessory glands* or *goiters* may develop. Sometimes the thyroglossal tract does not terminate in the thyroid but extends downward into the anterior mediastinal space, and may even reach the aorta. In that case accessory glands may be left over the entire length of this course the origin of accessory thyroid glands, and of tumors of the mesobranchial type, developed not only in the tongue and in the cervical region but also in the mediastinal space. Thus is explained the origin of the thyroglossal cyst occurring below and above the hyoid bone and of all the thyroid tumors found in the tongue.

In the same way during the embryological evolution islands of ectodermic epithelium may be left behind, remaining in close contact with the thyroid gland. Later on these inclusions are liable to give rise to tumors with pavementous epithelium, hence, canceroid of the thyroid.

The dorsal cul-de-sac of the third branchial groove forms the *external* or *thymic parathyroid*. The ventral portion of this third groove forms the *internal parathyroid*. The ventral cul-de-sac of the fifth branchial groove forms the *postbranchial* or *ultimobranchial body*.

**Postbranchial Bodies.**—Van Bemmelen discovered in the embryo of the shark and thornback, behind and on each side of the last branchial arch, a pocket-like formation containing follicles, resembling the thyroid gland. This glandular organ lies so near the heart that Van Bemmelen called it *supraparacardial body*. With the exception of the cyclostoma and the temnostiver such organs have been found in other classes of vertebrates, for instance in the amphibious reptiles, birds and mammalian animals. Because these organs are always situated behind the last branchial arch, Miwa called them *postbranchial bodies* (Fig. 7). In amphibious reptiles, birds and mammalian animals these

postbranchial bodies give rise to follicles with epithelium and vibratile cilia, but according to Miwa colloid is never found.

These colloid bodies have been considered by a few authors as giving rise to the lateral thyroids, which after fusion with the median thyroid were thought to form the thyroid gland. But this has been disproved by Miwa, His, Verdun and Tourneux. In their opinion these postbranchial bodies have nothing to do with the formation of the thyroid gland. They are separate organs whose significance is not yet clear. In Verdun's judgment they undergo an atrophy and finally disappear.

#### EMBRYOLOGICAL CLASSIFICATION OF THE THYROID TUMORS.

From an embryological standpoint, De Quervain, Delore and Almartine were consequently justified in classifying the thyroid tumors in two large classes:

I. Tumors of mesobranchial origin.

II. Tumors of branchial origin.

TUMORS OF MESOBRANCHIAL ORIGIN.—These are median tumors in the neck which originate from the thyroglossal duct and from the organs which derive from it, namely, the thyroid gland and the accessory thyroid glands.

- |   |   |   |
|---|---|---|
| 1. From the <i>thyroglossal</i> duct.         | { | a. Lingual goiter.  |
|   |   | b. Median, congenital cyst and fistula; benign and malignant. |
|   |   | c. Goiters with cylindrical epithelium.                       |
| 2. From the <i>thyroid</i> itself.            | { | a. All benign goiters.  |
|   |   | b. All malignant goiters.                                     |
| 3. From the <i>accessory thyroid glands</i> . | { | a. All benign accessory goiters.                              |
|   |   | b. All malignant accessory goiters.                           |

#### TUMORS OF BRANCHIAL ORIGIN.

- |  |   |   |
|--|---|---|
| 1. Tumors of <i>ectodermic origin</i> due to inclusion of ectodermic epithelium. | { | All cancers with pavementous epithelium.  |
|  |   |   |
| 2. Tumors of <i>endodermic origin</i> due to inclusion of endodermic epithelium. | { | a. First branchial groove gives the <i>fistulæ</i> in connection with the external auditory canal and the <i>mixed tumors</i> developed in the parotid and submaxillary glands. |
|  |   | b. Second branchial groove gives <i>branchial cyst</i> and <i>fistula</i> and all mixed tumors of the lateral region of the neck.   |
|  |   | c. Dorsal portion of the third and fourth grooves gives <i>parastruma</i> .   |
|  |   | d. Ventral portion of the fourth or fifth branchial grooves gives the postbranchial tumors.   |

This synoptical picture based on embryological considerations is very clear and scientific. It gives the key to the explanation of these very obscure tumors found in the neck and in the thyroid gland, which have so long been a puzzle to the pathologist. Easily explained thereby will be the origin of lingual goiter; of the median and lateral cysts and fistulæ of the neck; of the accessory glands from all along the neck and in the superior portion of the mediastinal space. Easily explained, too, are these puzzling and various tumors in which the thyroid is so rich, as the parastruma, papilloma, postbranchial, mixed tumors, etc.



## CHAPTER II.

### PHYSIOLOGY OF THE THYROID.

**History.**—Theories regarding the physiology of the thyroid have been numerous. Wharton thought it was merely a cosmetic organ whose function was to produce a nice, soft, roundness of the neck. Other authors thought that it acted as a mechanical support to the larynx, and protected this organ against cold. Boerhaave thought that it acted as a cushion whose gentle pressure served as a modulator of the voice. Morgagni, Santorini, Winslow and Lalouette thought that the gland was in direct communication with the larynx, and that it probably had an excretory canal emptying into the region of the vocal cords; and that under such conditions the secretion of the thyroid acted as a lubricant for these cords. As late as 1870 Ricou believed in the existence of this excretory canal; some other authors believed that the thyroid communicated directly with the esophagus and considered the foramen cecum as the point of outlet of the canal.

For quite a long time the thyroid was considered as a mechanical regulatory organ of the blood circulation and was regarded as an arterial reservoir intercalated between the cephalic and the carotico-subclavian systems; filled with blood, the gland was thought capable of compressing the carotids, thus diminishing the quantity of blood going into the brain. Compared to a sponge capable of derivating or giving up at will the blood destined to the cerebral organs, the thyroid was then regarded as a safety-vent for the cerebral circulation. There is no need to say that these hypotheses are for the most part purely fanciful and are not supported by any experimental facts. However, it might be incorrect to claim that the thyroid has no effect whatsoever on the cerebral circulation, as this gland receives its nerve supply from the superior laryngeal nerve containing the vasodilator fibers, and from the sympathetic nerve which contains the vasoconstrictor fibers. Experimentation shows that excitation of the central end of the superior laryngeal nerve causes an intense reflex vasodilatation of the thyroid: hence diminution of the quantity of blood directed toward the cerebrum; on the other hand, irritation of the sympathetic nerve causes a vasoconstriction, and consequently an increase of the quantity of blood thrown into the cerebral circulation. It is therefore possible that in certain given conditions this mechanism is called into play and thus

may be regarded to a certain extent as a regulator of the cerebral circulation.

One of the most curious theories of the physiology of the thyroid was that of Fomeris. According to this author this organ played an important part in the physiology of sleep; it swelled up during sleep because it retains a certain portion of the blood destined to the brain and gives it off again during the period of wakefulness. Evidently the author believed that sleep was due to cerebral anemia.

In conclusion we may say that the regulation theory is not supported by any experimental facts nor by surgical experience, as no disturbances in the cerebral circulation are noticed after operations. The histological structure of the gland, too, speaks against this theory; the thyroid is a glandular and not a cavernous organ. In fact all these theories have only a historical interest. It is only in the last quarter of a century that our knowledge of the physiological function, although still incomplete, has become more precise; the thyroid must be regarded as a glandular organ of great importance in metabolism.

In 1840 Astley Cooper noticed that thyroidectomy in animals was followed by a peculiar symptom-complex, but he did not pursue his experiences any further nor did he give his observations their correct interpretation. In 1859 Schiff called attention to the dangers connected with thyroid insufficiency. His experimental results, however, passed unnoticed until 1883, when Kocher and Reverdin made their epoch-making discovery.

The physiology of the thyroid may be studied from two angles. Valuable information may be gained by performing a complete thyroidectomy in animals to see what the outcome will be. Information may be, furthermore, secured by studying the influence of the administration of the gland itself upon the different organs and functions of the body.

**Results of Experimental Thyroidectomy.**—The thyroid is an organ necessary to life and its absence produces a clinical syndrome which has been called *myxedema* or *cachexia thyreopriva*, and which terminates, as a rule, in death. Schiff, Wagner, Horsley, von Eiselsberg and others have shown that extirpation of the thyroid in young animals causes death much sooner than extirpation in adults. Children with total aplasy of the thyroid never reach puberty. The most important symptoms observed after complete thyroidectomy are a retarded metabolism and an arrest in the growth of the osseous system, myxedematous infiltration of the skin and intellectual disturbances.

In *young animals* the arrest of development is considerable and affects at the same time the skeleton, the nervous system and the genital apparatus. Young thyroidectomized animals remain small; their bones do not develop; their cartilages and epiphyses do not proliferate; they

retain, in fact, their fetal aspect. The skin becomes rough and infiltrated with a mucinoid substance, hence the name *myxedema*. This mucinoid infiltration is found, too, in muscles, nerves and other organs. The young animals remain apathetic and dejected; their movements are slow and awkward, while physical activity is a burden to them. The genital organs remain infantile; the testicles do not descend and, as a rule, do not secrete spermatozooids; the ovaries remain small and become sclerocystic. Furthermore, the respiratory exchanges and oxidation processes are diminished; the animals become anemic; their temperature is low and the development of the disease is progressive until death occurs.

In 1917, Hoskins and Morris removed successfully the anlage of the thyroid gland from young growing larvæ of *R. sylvatica* and *Amblystoma punctatum*. The stage best suited for these experiments is that just preceding the beginning of the circulation of the blood. Thyroidectomy was performed in 14 frog larvæ and 50 amblystoma larvæ, checked against an equal number of control animals. A few of the thyroidectomized frog larvæ developed abnormally shaped external gills. One animal developed no external gills, although it lived and grew through a period during which external gills normally exist. The operated animals grew less rapidly than the controls. Only 1 control and 1 experimental animal survived the normal period of metamorphosis; of these the controls showed hind legs two months after the operation while the others had not developed legs four months after operation.

Serial sections were made of 8 experimental frog larvæ. It was seen that the operation had prevented development of the thyroid gland in all but 1 case. The hypophysis as compared with that of the controls showed no changes in size or structure that could be attributed to the loss of the thyroid gland.

Among the amblystoma larvæ none developed abnormal gills. The average growth-rate of the experimental larvæ was less than that of the controls, but of the 14 which were alive after three months the largest did not have the thyroid removed. In none of the 13 animals that were successfully operated was there any regeneration of the thyroid. There were no changes in the hypophysis nor in the pigmentation of the skin following thyroidectomy during three months in which the operated larvæ were under observation.

A complete thyroidectomy in *adult animals* produces the same clinical picture, but less intensified. The muscular system becomes weak and paretic; the nervous and psychic functions are disturbed; the skin becomes swollen and edematous, while the hair becomes dry and brittle. The metabolism is diminished, but as these animals have reached normal growth no disturbances of the osseous system are found.

Food seems to have a certain influence on the severity of the development of myxedematous conditions. Thyroidectomized dogs, for instance, seem to stand a cooked-meat diet with impunity, but as soon as they are given fresh meat the symptoms of thyroid insufficiency at once become more severe. Death can be delayed for a longer period if the animals are kept on a milk diet. Apparently, thyroidectomized animals are unable to destroy certain toxic products of a meat diet.

After the thyroid has been completely removed, its functional insufficiency becomes manifest more or less rapidly, sometimes in a few days, sometimes after a few weeks, and sometimes after many months. For instance, Tizzoni, Alonzo and Ughetti did not observe symptoms before nine months, and Horsley waited one and three-quarters years before symptoms of cachexia appeared in a sheep which had been completely thyroidectomized. This will explain why there have been authors claiming that total thyroidectomy had no effect upon the condition of the animals. Either these authors did not wait long enough for myxedematous symptoms to appear or they mistook the lymphatics or submaxillary glands for the thyroid, or if they did remove the thyroid, their operation was not complete, or if it was, accessory thyroids must have been present.

**Thyroid and Parathyroids.**—For a long time great confusion has prevailed concerning the correct interpretation of phenomena observed after thyroidectomy, as symptoms depending solely upon the thyroid insufficiency were ascribed to parathyroid disturbances, and *vice versa*. It was thought, too, that the consequences of thyroidectomy were more severe in certain species of animals than in others. Horsley, in 1891, summing up the results of experimental pathology, found that thyroidectomy was not followed by cachexia in birds and rodents, that it took a mild course in ruminants, and that it was of the utmost severity in carnivorous animals. To be sure, everything being equal, symptoms following total thyroidectomy in carnivorous animals are more severe than in herbivorous animals, because, as we have seen, a meat diet seems to cause more symptoms than a milk or herbivorous diet, but this is not the sense of the above statement. Horsley meant that carnivorous animals became acutely sick and died after a few days in the most acute convulsions, whereas herbivorous animals stood the operation more easily and developed gradually a chronic pathological condition known as myxedema. As we see, he did not at the time differentiate the symptoms belonging to thyroid insufficiency from the ones of parathyroid origin.

*Thyroid* and *parathyroids* are not only anatomically and pathologically different, but their physiological function is likewise not similar. If in animals the thyroid alone is removed and the parathyroids left *in situ*, a chronic, slow cachexia, which we call *myxedema*, takes place;



but if the parathyroids alone are removed and the thyroid left *in situ*, the most severe convulsions appear very soon and the animal dies of *tetany* in the course of a few days. Now, then, the error made in the interpretation of these symptoms can be very easily explained. In carnivorous animals the parathyroids are found, as a rule, embedded within the capsule in the thyroid tissue itself, while in herbivorous animals the parathyroids are located outside the capsule of the gland. In sheep and goats, for instance, a considerable amount of parathyroid tissue is present outside of the thyroid gland; in rabbits two of the parathyroids have no relation whatsoever with the thyroid. Consequently, when thyroidectomy was performed in carnivorous animals, the parathyroids were removed *ipso facto* at the same time, whereas in herbivorous animals they were left uninjured; hence the difference in the clinical picture in both species of animals. In one case they developed *tetany*, in the other *myxedema*.

Pineles, on the strength of his clinical researches on congenital absence of the thyroid, had already come to the conclusion that the parathyroids and thyroid were two entirely different organs, anatomically as well as functionally. In his judgment, if Nature wanted to undertake an experiment to demonstrate the independence of the parathyroid system from the thyroid one, it could not have done it more elegantly and more fully than in *thyroid aplasia*. We know that in such condition the thyroid is entirely absent, while the parathyroids are preserved. In 8 out of 14 cases of thyroid aplasia he was able to demonstrate microscopically the absence of the thyroid and the presence of normal parathyroids. Furthermore, he showed that in 4 cases of lingual goiter which had been operated, myxedema followed, whereas no symptoms of tetany were observed, for the simple reason that in such cases every bit of thyroid tissue had been removed, while the parathyroids had remained untouched.

To Gley, Vassale and Generali, however, belongs the credit for having demonstrated beyond doubt that the symptoms observed in animals after strumectomy did not all recognize the same origin, and that nervous symptoms and convulsions were due to an injury of the parathyroids, whereas myxedema recognized as its cause a thyroid insufficiency. Since then these conclusions have been investigated and controlled by a great number of authors and found correct. We can today safely conclude that the thyroid and parathyroids are two entirely different organs, and that to the insufficiency of one organ belongs a set of symptoms which differ entirely from the clinical picture due to insufficiency of the other one. Such conclusions are based upon the following reasons: After partial extirpation of the parathyroids, tetany does not occur; no lesions of the nerves in the neck, as extensive and

complicated as they may be, can determine similar symptoms; furthermore, histologically, the parathyroids are different from the thyroid. If the thyroid alone is removed no tetanic convulsions develop, but myxedema follows; if the parathyroids are removed and the thyroid is left untouched, the clinical picture of parathyroid insufficiency at once becomes acute, but no myxedema follows. The trophic disturbances are due to the absence of the thyroid alone, whereas the acute, convulsive troubles must be referred to the suppression of the parathyroid function. Furthermore, in athyroidism the thyroid function alone is suppressed, whereas the parathyroids remain normal. In postmortems of myxedematous patients and cretins where no vestige of the thyroid could be found the parathyroids were found normal. Finally, parathyroid opotherapy is often capable of curing tetany, whereas thyroid opotherapy is inefficacious.

I know that on the strength of certain experiments made by Gley in 1909-1911, by A. E. Melnikov in 1909, by Iselin in 1911 (who found that young parathyroidectomized animals which did not succumb to tetany developed a condition similar to rickets and died of cachexia), by Louis Morel in 1911 (who seems to have demonstrated that after parathyroid extirpation symptoms of slow cachexia similar to the one seen in myxedema develop), Gley, in the last edition of his *Physiology*, 1913, believes there must exist a functional association between these two organs. According to these authors tetany is not the only consequence of the parathyroid insufficiency, but the suppression of these glandules determines cachexia and trophic disturbances of the skeleton, probably by disturbing the entire chemical metabolism. How? It is not known. Swale, Vincent and Joly do not want to admit that the parathyroids have a specific function of their own. They believe that the thyroid and the parathyroids form a unique, physiological system, that the thyroid is capable of a vicarious function in case of parathyroid insufficiency, and *vice versa*. They seem certainly contradicted by the clinical and experimental facts.

**Postoperative Tetany in Animals.**—The symptoms due to complete parathyroidectomy develop soon after operation and are rapidly fatal. Localized or generalized *tetany* is the dominant symptom. A few hours or a day or two after parathyroidectomy has been performed symptoms begin; the gait of the animal becomes unsteady and awkward; an intense tremor develops and later on clonic muscular contractions, tetanic cramps, resembling the contractions seen in tetanus, dominate the picture. Resting apparently quietly for a time the animal is suddenly taken with a convulsive spell, falls on his side, with teeth chattering; rigidity may or may not be present; a few minutes after, everything is over. These spells gradually recur more frequently and the spasmodic

contractions become more intensely developed. During the convulsions the animal cries, showing that he suffers; his hind legs are contracted and stiff and in the most severe cases the animal may lose consciousness for hours. During the spell his temperature rises very high and may reach 109–110°. Respiration is accelerated. During the spells dyspnea is very marked; tachycardia is present; urine is scarce and often contains albumin. The number of red corpuscles is diminished, whereas the polynuclears are increased. Death occurs, as a rule, five to eight days after parathyroidectomy, and takes place during convulsions or coma.

If one parathyroid has been left *in situ*, tetany does not follow or may appear only temporarily. This is so true that Halsted was able, in a very elegant and conclusive experiment, to show that the removal of the four parathyroids in an animal was absolutely harmless, provided that one of these glandules was transplanted into the abdominal wall. The animal lived without showing any pathological manifestations whatever. But as soon as the transplanted parathyroid was removed, marked symptoms of tetany soon appeared and death followed quickly. In some instances tetany developed, although one parathyroid had been left *in situ*. This was probably due to the fact that the little glandule had been unduly traumatized or disturbed and had gradually undergone resorption. If removal of the parathyroids is done gradually and at different periods of time, as soon as the whole parathyroid system is removed the symptoms become just as acute as if all the parathyroids had been suppressed in one sitting. Although the symptoms are less marked in adults than in young animals, the termination is nevertheless fatal in both. It is during pregnancy that parathyroid insufficiency presents its maximum of development. Adler and Thaler have shown experimentally that the removal of a small portion of the parathyroids in pregnant animals caused severe symptoms of hypoparathyroidism, whereas the removal of the same amount of parathyroid tissue in non-pregnant animals was without effect.

Iselin showed that the offspring of rats which had undergone experimental lesions of the parathyroids showed a marked congenital tendency to tetany. This latent parathyroid insufficiency was so marked that the removal of one parathyroid only was sufficient to determine the most violent tetany, which always proved fatal.

Pfeiffer and Mayer found in the blood of dogs suffering from post-operative tetany a toxic principle which injected into mice did not cause any disturbance whatever until the parathyroids of these mice had been subjected to trauma. In that case, even if a large portion of the parathyroids were left uninjured, the mice developed the most severe tetanic symptoms, whereas the controls remained unaffected.



For fuller information see: Postoperative Tetany in Surgical Technic.

**Action of Thyroid Administration and Thyroidectomy on Metabolism.**—Under normal conditions the thyroid secretion is a physiological product playing a very important part in metabolism and elaborated in sufficient quantities to meet the physiological demands of the organism; but as soon as it is secreted in excessive or insufficient amount, marked pathological symptoms follow; hence, *hyperthyroidism* and *hypothyroidism*.

Experimental evidence is presented by W. W. Swingle in support of his hypothesis that the long period of larval life of certain species of anurans (*Rana catesbiana*, for example) is due to the slow rate of thyroid development. Grafting of the thyroid glands of advanced second-year tadpoles into small, immature first-year tadpoles produced rapid growth in the latter up to the stage of development shown by the animals from which the glands were obtained.

From the beginning of opotherapy it has been observed that if thyroid preparations are given to animals or human beings, a certain train of toxic symptoms which we call *acute thyroidism* may sometimes follow, as tachycardia, headache, vertigo, mental excitation, tremor, nausea, vomiting, polyuria, albuminuria, glycosuria and moderate exophthalmos. The symptoms observed in such conditions are of two varieties: (1) the ones due to the physiological properties of the thyroid itself; (2) the ones due to adulterated thyroids. This latter condition will be discussed in the chapter on Opotherapy.

Some of the symptoms found in acute thyroidism are very similar to those found in iodine intoxication, as cerebral excitation, palpitations, tremor, etc. Ewald believes that a certain number of symptoms seen in acute thyroidism may be due to the excessive or rapid phenomena of disassimilation and to the direct action of the drug on the nervous centers. Thyroid extract injected into normal animals produces at first prostration and somnolence, and soon after tachycardia, tremor, fever, dyspnea, extreme agitation, brilliancy of the eyes, slight exophthalmos and polyuria. Gradually the animals lose flesh, have diarrhea, melena, polyuria, albumin, and finally sink into a state of stupor, become semiparalyzed in their hind legs and die. Young animals succumb very much sooner to hyperthyroidization than adult ones. Ballet saw a young dog, five or six months old, die seven days after daily intravenous injections, whereas adult animals could stand doses three times as large for months.

In certain instances thyroid extract being used in subcutaneous injections, the same authors could witness the development of a real, experimental goiter. Lanz and Trachewski were able to produce an atrophic thyroiditis with thyroid feeding. For further details see chapter on Etiology of Thyrotoxicosis.



Injected subcutaneously, intravenously, or given by mouth, thyroid extracts have more or less the same influence on *previously thyroidectomized* animals. Trophic disturbances gradually diminish; myxedema becomes less marked; the skeleton grows again; the metabolic exchanges increase; blood becomes normal; urine is secreted in greater quantities, and, in short, the animals have a tendency to become normal again.

**Thyroid and Heat Regulation.**—In bats during hibernation the colloid of the thyroid disappears and the whole gland shows a largely diminished function. If thyroid extract is injected into a hedgehog during hibernation, one and a half hours after the injection, respiration becomes more frequent and approximately three hours after the animal gets up and runs around. Extracts of other organs have no influence, except possibly extracts of thymus. A remarkable symptom in the hedgehog is that after the injection of extract of thyroid the temperature rises from 9° to 30° C.

**Action of the Thyroid on the Cardiovascular System.**—In 1895 Schöefer saw that an intravenous injection of thyroid extract lowers the blood-pressure and causes a marked dilatation of the peripheric bloodvessels. As this has been found correct by many authors since, the thyroid gland has been regarded as an organ producing vascular hypotension. The theories set forth to explain this physiological phenomenon have been various. Von Cyon sought to explain it by the “depressor nerve theory.” In collaboration with Ludwig he found in the cervical region of the rabbit a small nerve formed by the junction of a branch coming from the sympathetic and one coming from the superior laryngeal nerve which, as we all know, is a branch of the vagus nerve. This nerve is called the “depressor nerve.” It extends downward into the thoracic cavity, reaches the heart and terminates in the endocardium of the ventricles and auricles, in the region of the pulmonary artery and aorta. Its fibers are centripetal; excitation of the peripheric end does not produce any effect, but irritation of the central end is painful and determines at once a fall in the blood-pressure, which is caused by a reflex dilatation of the abdominal vessels. At the same time the heart action becomes retarded. If the two vagi have been cut, the excitation of the depressor nerve has no more influence over the heart action, but produces, just the same, a fall in the blood-pressure. According to its discoverer the function of the depressor nerve is to protect the heart against a sudden increase of pressure in the aorta and pulmonary artery. As soon as the blood-pressure exceeds certain limits the depressor fibers, terminating in the endocardium, transmit at once the irritation to the centers of the splanchnic nerves, either inhibiting the vasoconstrictor centers or intervening directly on the vasodilator’s centers. This causes at once a vasodilatation of the abdominal system. On account

of the enormous capacity of this system the blood is deflected from the heart and consequently the blood-pressure on that organ becomes reduced, hence the name *depressor* given to that nerve; at the same time the cardiac action becomes slower. "Therefore," says von Cyon, "the depressor nerve should be regarded as a means of defense of the heart."

At the same time, through its vagal portion, the depressor nerve puts the heart and the thyroid gland in direct communication, so that a mutual and direct influence of one organ upon the other is established. Furthermore, it seems to be an accepted fact that iodothylin and thyroglobulin increase the excitability of the vagus and depressor nerves, whereas they diminish the excitability of the cardiac accelerators. There seems to be no doubt in von Cyon's mind that this fall in blood-pressure takes place through the depressor nerve.

According to Carnot and Georgiewski the fall in blood-pressure cannot be the consequence of the bulbar or spinal paralysis of the vasoconstrictor centers, as it takes place after the bulb and medulla oblongata have been destroyed. Neither can it be a question of paralysis of the peripheric abdominal vasoconstrictor centers, as it takes place after ligature of the abdominal organs. The fall of pressure subsists after both vagi have been paralyzed with atropine. Very likely, according to these authors, it is due to direct action of the thyroid secretion on the cardiac musculature.

More recently Fürth, Schwarth, Gautrelet and Lohmann have thought that the hypotensive action of the gland was due to *choline*. This substance, however, is not found only in the thyroid but also in all the other organs. Lohmann found in the thyroid three substances: one which he called *arginine*, without action on the pressure; another which he called *histinine*, markedly hypertensive; and another decidedly hypotensive.

In 1913, Blackford and Sanford in examining the sera from patients with non-hyperplastic thyroids found that no depressor action was present.

The action of the thyroid secretion on the heart, according to Haskovec and others, causes a marked tachycardia, increasing with the slightest effort. This marked acceleration persists even if both vagi nerves have been cut. The frequency of cardiac trouble in goitrous patients is well known, and will be discussed at length in the chapter on Goiter Heart.

**Action on the Blood.**—Soon after complete thyroidectomy in animals a marked anemia is found; the red corpuscles diminish and leukocytosis takes place. It was on account of this anemic condition that the thyroid was for a long time considered as a hematopoietic organ.

After thyroidectomy the blood becomes intensely "venous," and according to Albertoni and Tizzoni in the most severe cases of thyroid insufficiency the amount of oxygen may sink below the half of the normal quantity; of course the amount of  $\text{CO}_2$  is greatly increased. It is to this venosity of the blood that Herzen, Vassale and Rogowitsch attribute the increased number of respirations of thyroidectomized animals. Vassale thinks that the red corpuscles have lost their capacity for fixing oxygen, because he found that soon after intravenous injection of thyroid extract the blood loses its venous properties and becomes normal again. This "anoxymia" may explain why thyroidectomized animals are so sensitive to slight changes in temperature. This is true, too, of patients suffering from cachexia strumipriva or of a mild degree of spontaneous hypothyroidism. We know that such patients prefer to be in warm rooms, and that even in the hottest day of summer they do not suffer from the heat.

The number of red corpuscles is materially diminished and so is the hemoglobin; polynucleated erythrocytes are not a rare feature. In such conditions the red corpuscles have a fetal aspect, are larger in diameter and contain several nuclei. In hyperthyroidism the red corpuscles do not show any modification in quality nor in quantity. Soon after thyroidectomy the leukocytes increase in number but diminish later on. In hyperthyroidism the number of leukocytes is reduced, but hyperlymphocytosis combined with hypopolynucleosis is present.

The blood serum of thyroidectomized animals possesses toxic properties, and according to Bianchi, Jacobi and Wassermann its bactericide power is diminished. This explains why insufficiency of the thyroid predisposes to infections. Pagenoff thinks that the toxicity of the serum is caused by a leukomain which probably is nothing more than the thyroproteid of Notkine.

**Action on the Nutrition.**—After thyroidectomy the nutritional disturbances are very marked. The animal's metabolism is reduced, the nitrogenous excretion is diminished, and in the skin a myxedematous infiltration takes place; this edema is hard, does not pit on pressure and is of a sallow color. According to Virchow this infiltration is caused by an active proliferation of the subcutaneous tissue and to the presence of mucine. In myxedema Horsley has found mucine not only in the skin but in the blood, muscles, carotids, etc. He considers the thyroid as an organ regulating the assimilations and disassimilations; in his judgment after removal of the thyroid these assimilatory processes do not take place any more, consequently, albuminates remain in their mucinoid state and are not metabolized.

The thyroid regulates the accumulation and repartition of fat in the body. It is well known that in hypothyroidism adipose tissue is



increased, whereas in hyperthyroidism it is diminished. Lately it has been demonstrated that the thyroid contains a *lipase* which in thyroid insufficiency is diminished, but is materially increased in hyperthyroidism, hence the intense lipolytic properties of the serum in Graves's disease. This lipolytic property is found not only *in vivo* but *in vitro*, as Youchtchenko has demonstrated.

**Action on the Osseous System.**—Trophic disturbances of the osseous system after total thyroidectomy are in direct proportion with the age at which the loss of thyroid function occurred: the younger the animal, the more intense the disturbances will be. The growth of skeleton ceases, bones remain short and fragile, calcification is incomplete and ossification of the cartilages is arrested. Bones of thyroidectomized animals compared with those of controls are seen to be at least a third smaller. As pointed out by Gauthier, the fact that certain fractures do not repair normally and that the callus formation is retarded for weeks and months may be recognized as the result of thyroid insufficiency. Thyroid opotherapy in certain of these conditions has proved, indeed, very successful. On the other hand, according to Holmgren individuals affected with exophthalmic goiter at the time of their growth appear to have longer bones than normally.

**Action on the Nervous System.**—In animals which have died following intensive hyperthyroidization no well-defined lesions of the nervous system are found, whereas the cerebrospinal lesions seen in thyroidectomized animals have been various and multiple. Albertoni and Tizzoni found peripheric neuritis; Weiss and Rogowitsch found anemia, edema of the nervous elements and a parenchymatous encephalitis; Schultze and Schwartz saw a leukocytic infiltration in the membranes surrounding the upper portion of the medulla. Herzen and Löwenthal saw a vacuolar degeneration and atrophy of the pyramidal cells and corticalitis of the region of the sigmoid gyrus, which is the motory center of the lower limbs. Capobianco reported vacuolar degeneration in both hemispheres of the cerebellum, in the bulb and in the gray matter of the medulla. Pisenti and Luppo found bulbar hemorrhages. Walter saw that thyroidectomy interferes with the regeneration of the peripheric nerve after traumatism, but that as soon as thyroid opotherapy is started the regeneration of the nerves takes place. Walter described marked pathological disturbances in the hypophysis after complete thyroidectomy.

Langhans has found a marked degeneration of the muscles in cretins. This degeneration is found, too, in Basedow's disease and may explain the muscular weakness and tremor found in this condition.

Extracts from the fresh pig thyroid gland were made under John Roger's direction in 1918 with distilled water, with slightly alkaline

normal salt solution and with alcohol. When tested upon dogs it has been found that distilled water extract is inert, but that the alcoholic extract and the non-coagulable portion of the saline extract produce quite definite and immediate reactions. In brief, this material is vasodilating; it increases the vigor of both voluntary and involuntary muscular contractions; it is a stimulant to the secretory activity of the pancreas and it increases gastric secretion and peristalsis. In the case of the stomach this stimulant or activating influence can be prevented or arrested by the injection of either atropine, which paralyzes the terminal filaments of the vagus, or of adrenalin, which is believed to stimulate the sympathetic or opponent of the vagus.

In these experiments no material could be found that would produce any appreciable degree of tachycardia. Furthermore, no material could be isolated from the human pathological hyperthyroid glands removed at operation which would produce any reaction whatsoever. A few tests made with extracts from normal human glands obtained at autopsy acted with the same vigor as the pig extracts. Hence, it looks as though the thyroid through its secretion activates or stimulates the autonomic or vagus group of nerves and not, as commonly believed, the sympathetic. The hyperthyroid gland, on the other hand, seems inert. At least no material could be isolated from these pathological organs which would produce any reactions.

**Modification of the Urine.**—In myxedema the quantity of urine is diminished and its toxic properties are increased. According to Pagenoff this toxicity of the urine is due to the same leukomycin which he found in the blood of thyroidectomized animals. In the urine and thyroid of Basedow's patients, toxic products have been isolated by Boynet and Silbert. The excretion of phosphorus in urine diminishes markedly after total thyroidectomy. Sugar, which is very often found in exophthalmic goiter, seldom appears in myxedematous conditions. It is well known that in Basedow's patients alimentary glycosuria is easily produced, whereas patients with hypothyroidism can stand large doses of sugar without showing glycosuria.

Albumin is sometimes found in great quantities after complete thyroidectomy, but Corronedi claims that albuminuria is caused by the fact that thyroid and parathyroids have been *simultaneously* removed, and that albuminuria is a symptom of parathyroid insufficiency and does not occur when the parathyroids have been left uninjured.

Robert Hutchinson in a revision of the literature upon the effects of thyroid extract on metabolism says: "It may be said that the effect of the administration of thyroid is to increase the oxidation of the body; it makes the tissues, as it were, more inflammable, so that they burn away more rapidly. The products of the disintegration of the nitrogenous

substances appear in the urine almost entirely in the form of urea, uric acid and the xanthin bases, while the products of the fat destruction are eliminated as  $\text{CO}_2$  by the lungs and as water by the kidneys."

Underhill and Faiki found that after complete thyroidectomy the ammonia output in the urine was increased even beyond what is observed in starving animals. Nitrogen in the urine is eliminated under the form of kreatin, purin bodies, allantoin. They found that thyroidectomized dogs are incapable of utilizing subcutaneously introduced dextrose in anywhere near the same degree as normal animals, that thyroid tissue fed to normal animals causes a slight increase in the urinary nitrogen excretion, and that this influence soon disappears when the thyroid feeding is stopped. Small doses of thyroid appear to have as pronounced an influence on nitrogen elimination as large ones.

**Eye Affections Following Experimental Thyroidectomy.**—Walter Edmunds while performing complete thyroidectomies and parathyroidectomies in animals observed 16 times a "ground-glass" appearance of the cornea, resembling a syphilitic keratitis and followed oftentimes by ulceration of the cornea with more or less affection of the eyeball. Tremor, spastic paralysis and convulsions were soon followed by death. In 19 other experiments in which one parathyroid and one lobe alone were removed, the other side being left intact, except that a considerable length of nerve supplying the thyroid and parathyroids was excised, Edmunds observed 5 times eye affections similar to those observed in total parathyroidectomies. Some eye changes have also been observed by Gley and Halsted.

**Conditions Affecting the Secretion of the Thyroid Gland.**—After connecting a galvanometer with the thyroid gland and the neighboring tissues, Cannon observed that stimulation of the sympathetic high in the thorax produced an electrical current, while stimulation of the vagus nerve caused no such current. Clamping of the bloodvessels supplying the thyroid did not cause any electrical changes. He therefore concluded that the sympathetic fibers of the thyroid gland may be reasonably assumed to be true secretory nerves. At the same time he observed that stimulation of the adrenals to increased activity causes a characteristic reaction of the thyroid. In experimenting on the cat, the anterior root of the right phrenic nerve was fused with the right cervical sympathetic, thus causing a volley of nerve impulses to the thyroid each time the animal breathed. In 4 of the animals which survived operation, symptoms and metabolic changes very similar to exophthalmic goiter in man were observed. All symptoms receded after resection of the right half of the thyroid was performed, hence, Cannon's conclusion that the thyroid is subject to that division of the nervous system which is brought into action during emotional excitement and

which causes adrenal secretion. This conclusion is based upon the claim that during emotional excitement the adrenals are stimulated into production of greater quantities of substances which liberate sugar in the urine, cause abolition of the muscular fatigue, dilatation of the bronchioles, inhibition of digestion and redistribution of the blood in the body, with rapid coagulation.

*How much of the thyroid is it necessary to leave in order to prevent symptoms of thyroid insufficiency?* (See chapter on Surgical Technic: How much thyroid tissue can be safely removed?)



## CHAPTER III.

### BIOLOGICAL CHEMISTRY.

IN the thyroid Ordtmann found 81.24 per cent of water, 17.66 per cent of organic matter, and 0.1 per cent of inorganic matter, of which iodine occupies the most prominent place.

After iodine had been discovered by Courtois, in 1812, Straub, of Berne, suggested that it was the active principle of the "toasted sponges" and "*æthiops vegetalis*," both of which had been used for centuries in goiter therapy. Ever since its discovery iodine has been universally employed in thyroid pathology. In 1895, very much impressed by the similarity of the effects of iodine and thyroid, Kocher suggested that it would be advisable to examine thyroids for that element. These researches, which were entrusted to an incompetent research worker, remained, however, negative. More fortunate than Kocher, Baumann in the same year discovered in the thyroid an element which he called *iodothylin* (thyroidin of Roos). This he considered as the active principle of the gland. Brown states that this amorphous substance resists the digestive ferments and is insoluble in a 10 per cent solution of HCl. Its iodine content varies from 10 to 14 per cent. This nitrogenous compound gives the xanthoproteic reaction. Later researches established the fact that this substance does not exist as such in thyroid, and that it is not the result of an active principle in the gland, but is produced artificially by the brutal action of sulphuric acid on the thyroid and is the result of decomposition of iodized substances contained in the gland.

Notkine extracted from the thyroid an albuminous substance which he called *thyreoproteid*. Given in subcutaneous injections to thyroidectomized animals it produces convulsions, dyspnea and death, whereas given to normal animals it causes symptoms resembling those of cachexia strumipriva. This substance is not normally found in the thyroid, but is a toxic product of metabolism, and is neutralized in the gland itself.

Hutchinson, in 1897, discovered in the colloid two different substances: a *proteic* one, scarcely active and containing very little iodine, and a *non-proteic* one, with energetic properties, and rich in iodine and phosphorus.

Oswald isolated from the thyroid two different substances: the *thyreoglobulin* and the *nucleoproteid*. The first one may contain iodine or may not. If it contains iodine, it is called *iodothyreoglobulin*. The



nucleoproteid is free of iodine but contains great quantities of phosphorus. Both substances enter for the most part into the composition of colloid. Normally, the human thyroid contains from 1 to 9 gm. of thyreoglobulin and its amount increases in direct proportion to the quantity of colloid.

When injected intravenously the nucleoproteid was found by Oswald and von Cyon physiologically inactive, whereas the iodothyreoglobulin possesses energetic properties. Its iodine content varies with the species of animal, 1.16 per cent in the hog, 1.86 per cent in cattle, and 0.34 per cent in the human being. When thyreoglobulin is free of iodine, as in young animals, it may be transformed into iodothyreoglobulin by adding an iodide compound to the food. This synthesis is possible in the organism only, as Oswald was unable to iodize the thyreoglobulin *in vitro*. In newborn babes whose mothers had been fed with iodine Nagel and Roos always found iodine in their glands, while they did not find any in the thyroids of babes whose mothers had not been fed with iodine during their pregnancy. Marine and Lenhart have recorded similar results for animals. The quantity of iodine contained in a gland is dependent upon the quantity of colloid and upon the quantity of thyreoglobulin contained in the colloid.

The quantity of iodothyreoglobulin which can be extracted from the thyroid amounts to a few grams and contains about 0.5 per cent of iodine. How much of this substance is daily secreted by the thyroid is extremely hard to say, but, according to Oswald, if we take into consideration the amount of iodothyreoglobulin which was sufficient to cure the case of myxedema reported by him we may judge that in the adult this amount will scarcely exceed 0.05, which contains about  $\frac{1}{30}$  mg. of iodine. The action of iodothyreoglobulin must not be compared with iodine, as the latter has entirely different pharmacodynamic properties. Iodine is an inorganic compound while iodothyreoglobulin is an organic albuminous substance.

The nucleoproteid of Oswald does not contain iodine but contains 0.16 per cent of phosphorus and arsenic. Besides these elements *leukomains* have been found by Bourquelot and Lepinois and *bromine* by Baldi. Chamagne was able to extract from the thyroid very toxic *lipoids*. Albumoses, leucin, xanthin, hypoxanthin, NaCl, sulphur oxalate of calcium and lactic acid are parts of the constituent elements of the thyroid.

The *dijodthyrosin* which Oswald discovered later has the characteristic elements of iodized albuminous substances, but has no effect on the circulatory apparatus nor on the nervous system, and does not influence goiter in any way, therefore it cannot be considered as the active principle of the thyroid.

**Thyroxin.**—Kendall, in 1914, was the first to isolate from the thyroid a crystalline substance (iodine, 60 per cent), the definite chemical formula of which was determined in 1917. It is locked in a protein molecule and can be obtained only by reaction of carbon dioxide upon the thyroid. This substance has been called "thyroxin" and has been shown to be trihydro-4, 5, 6, tri-iodo-2-oxy-beta-indolpropionic acid. It possesses the same physiological action as the gland itself and was synthesized in 1919. Its chemical formula is  $C_{11}H_{10}O_3NI_3(C_{11}H_{10}O_3NI_3)$ . According to Kendall, the thyroxin content in the tissues of the normal person is as constant as is the number of red blood cells. The total amount of thyroxin in the tissues of the body is about 13 mg. By alkaline alcoholic hydrolysis Kendall separated the thyroid proteins into two groups: the *Group A*, soluble in acids; and the *Group B*, insoluble in acids. By continued hydrolysis, the Group A compounds were further separated and in final analysis the crystalline iodine-containing thyroxin obtained. Although containing about half of the total iodine found in the thyroid proteins, no definite crystalline compound was obtainable from the Group B. This latter group does not contain thyroxin.

Physiologically speaking, the Group B does not produce any toxic effects, while Group A produces all the symptoms observed in hyperfunction of the thyroid. The severity of these symptoms is in direct proportion to the amount of iodine contained in the intermediary compounds up to the crystalline form. The amount of A-iodine compound necessary to produce symptoms is extremely small. One-half milligram per day produced marked symptoms in a cretin. Cardiac, nervous hyperactivity, as well as increased general metabolism, are observed. When administered to hypothyroid patients, thyroxin exerts as favorable an influence as thyroid extract itself. Normal animals treated with this compound show the striking effects of metabolic stimulation parallel to the effects of thyroid intoxication.

Thyroxin is a white crystalline substance which has the properties of a very weak acid. It is extremely insoluble in water, about 1 part in 1,000,000 parts of water, but it is readily soluble in sodium hydroxide. The most striking characteristic of thyroxin is its iodine content. The substance contains 65 per cent of iodine, which is very firmly attached to the organic nucleus and is not easily broken off with sodium hydroxide, although it is very easily broken off by the action of sunlight.

Thyroxin is extremely insoluble in acids and the first impure precipitation with acids contains approximately 10 per cent of iodine, although the original fresh gland contains only 0.04 per cent, that is, the thyroxin is 250 times more concentrated in this precipitate than it is in the gland.

Kendall says that the chemical reactions which concern thyroxin

are centered about the amino group and that it seems probable that its function is to permit the actions involving the acids and alkalies to take place at a faster rate. He claims that thyroxin has a direct intracellular effect throughout the body, acting as a catalytic agent, exchanging carbon-dioxide for amino-acids, then returning to the thyroid without losing its iodine content. It acts solely by increasing the metabolism.

Plummer states that thyroxin determines not only the quantum, but the rate also at which any particular cell can produce energy, so that the thyroid is entirely related to the production of energy in the body. It is a powerful activator of general metabolism.

Plummer says: 1. "After the administration of a single dose of thyroxin, sufficient to bring the basal metabolism to normal, the physiological status of a thyroidless patient becomes normal in from ten to twelve days, remains approximately normal for ten days and returns to the preëxisting status in from five to seven weeks.

2. "The amount of thyroxin in the tissues (exclusive of the thyroid) of the average normal man is approximately 14 mg. Kendall, from an analysis of the iodine content in the tissues, recently estimated the amount to be 14 mg.

3. "The average daily exhaustion of thyroxin in the tissues is between 0.5 and 1 mg.

4. "A shift of 1 mg. of thyroxin in the tissues of the body is accompanied by a corresponding rise or fall of between 2 and 3 per cent in the basal metabolism.

5. "Fourteen milligrams of thyroxin given to a thyroidless person is not fully exhausted until from the end of the fifth to the eighth week.

"Two milligrams of thyroxin a day may hold the basal metabolism from 20 to 30 per cent above normal; 3 mg. a day may hold the basal metabolism 50 per cent above normal.

"Fifteen milligrams of thyroxin given intravenously to patients with exophthalmic goiter who have a basal metabolism above plus 65 may not cause any noticeable reaction; when given to patients having large colloid goiter with bruit, the bruit disappears and the thyroid shrinks rapidly, but constitutional reaction may be absent. With these two exceptions a sustained elevation of the basal metabolism has followed every intravenous dose of more than 1 mg. of thyroxin.

"There are approximately 10 mg. of thyroxin in 150 grams of desiccated thyroid.

"A daily oral dose of 1.6 mg. of thyroxin will hold the basal metabolism of most thyroidless individuals within the normal limits."

**Iodine in the Thyroid Gland.**—Iodine is found not only in the thyroid gland, but can also be detected in a great many other organs, as the muscles, suprarenal bodies, hypophysis, liver, kidneys, central nervous

system, thymus, spleen and lymph nodes. We must admit, however, that it is present in the thyroid in larger quantities than in any other organ of the body except in the parathyroids. There, according to Gley and Lafayette, the quantity of iodine is even larger than in the thyroid.

Iodine in birds, mammals and fish is for the most part contained in the thyroid alone, although in certain fish it has been found in the oil glands, as, for instance, in cod-liver oil. Using the modified Baumann-Hunter methods, Marine was not able to recognize traces of iodine in the amphioxus, butter fish and weakfish, from which the thyroid area had been removed.

A. T. Cameron has published the findings of relatively large amounts of iodine in the thyroids of rays and dog fish.

Iodine varies with the conditions of life of animals as well as of patients; it varies, too, with localities. In Fribourg, Switzerland, for instance, where goiter is frequent, Baumann found only traces of iodine in 7 out of 26 glands. Their average content was about 2 mg., whereas 10 out of 27 glands from Hamburg contained more than 4 mg. In Berlin the quantity was found to vary from 5.3 to 8.1 mg. This difference was more striking in children. Out of 17 children of Fribourg from one day to seven years old only traces were found. Five times the thyroid contained a quantity of iodine varying from 0.7 to 0.3 mg., whereas in 5 thyroids of children from Hamburg, iodine was constantly present in proportion of 0.1 to 0.45 mg.

Iodine content in the thyroid increases if the food contains iodine. The aliments which contain most iodine are asparagus, carrots, beans, mushrooms and fish. Iodine medications increase, too, the iodine content of the thyroid. After the skin of a dog had been rubbed with iodoform, Baumann found that the thyroid gland of this dog contained 0.3 mg. Smith and Broders found that external applications of tincture of iodine increased to a considerable extent the iodine content of the gland, and that iodide of potash given internally or hypodermically increased the iodine content of the gland very materially. After ingestion of bromides, brome is stored in the thyroid in the same way as iodine. The amount of iodine in the thyroid increases gradually up to middle age and then decreases with old age. Atherton Seidell and Frederick Fenger found (*loc. cit.*): "That a marked seasonal variation existed in the percentage of iodine present in the healthy, normal-sized glands of the sheep, ox and hog. There is in general about three times as much iodine present in the months between June and November as in the months between December and May. The seasonal variation in the size of the glands was observed in the case of the sheep and ox, but not in that of the hog. The glands were found to be larger in the months during which the lower iodine content was noticed."



Iodine is not invariably present in the thyroid. Miwa, Stoeltzner and Baumann and other investigators have pointed out the frequent absence of iodine in the thyroids of children, of dogs fed on meat and in those of cattle and other animals. They believe that iodine found in the thyroid has no more significance than the traces of copper found in the liver, and that its presence or absence and its quantity are dependent upon the food of the animal. In herbivorous animals iodine is found in greater quantities than in carnivorous animals, because vegetables contain iodine in a more or less great quantity; whereas no iodine or very little is found in carnivorous animals, since pure meat diet contains no iodine or very little. Animals fed near the sea show a double amount of iodine than do those pastured in inland regions, because vegetable food along the coast is richer in iodine than that found in the interior. Töpfer, of Vienna, found no iodine in the thyroids of cattle; Roos, none in the thyroids of dogs, none in that of the wildcat, none in that of the polecat, and found it in but 2 out of 6 martens. It was absent from the thyroids of 4 domestic cats and traces only were found in those of 5 others. None was found in 4 out of 11 dogs nor in 2 out of 4 horses. Weiss after examining the thyroids of 7 children under four and a half years of age found that the iodine content varied from traces to 0.37 per cent. Wells in analyzing the thyroids of 6 children from Chicago found that the glands of 3 had from traces to 0.092 per cent; the other 3 had 0.11 per cent. Von Rositzky noticed in children under ten years of age that iodine in the thyroids varied from 0.012 to 0.041 per cent. Oswald in 5 children from Basel under seven years of age found from traces to 0.16 per cent. Charrin and Bourcet found in the thyroids of infants under three months from 0.0004 to 0.0054 per cent. Mendel found no iodine in the thyroids of 4 infants and found 0.07 mg. in others. Jolin found in 27 children from Sweden under four years of age no distinct traces of iodine and in 7 cases from traces to 0.086 per cent. Nigel and Roos found no traces of iodine in the thyroids of 4 newborn puppies. Yet animals as well as human beings in which iodine was totally absent or found in traces only were in just as good condition as the ones whose thyroids contained a higher percentage of iodine. Never have the children or animals in which iodine proved to be absent shown any indication of thyroid insufficiency. The hen's egg does not contain iodine when the young chick begins its life, yet its development seems to go on normally. The same is true for the human newborn. It is not possible to detect any pathological difference between animals which have a high percentage of iodine in their thyroids and those which contain none. The thyroid free from iodine seems to meet the needs of the body just as well as the thyroid which contains iodine. Thyroidectomy is followed by as severe symptoms in the latter case as in the former.

Therefore many authors conclude that iodine is not necessary for the physiological activity of the gland, that it is not the active principle of the thyroid, and that it is only an accidental constituent of its secretion. Hutchinson corroborated these conclusions. After having prepared an artificially iodized nucleo-albumin from the thymus of the calf, samples of which contained from 4 to 7 per cent of iodine, he found it inactive in the treatment of myxedema and without effect upon the pulse, temperature or weight of the subjects to whom it was administered. Blum and Hellin also found that iodized albumin was physiologically inactive. They consequently concluded, too, that iodine does not play any important part in the physiological function of the thyroid. Because an organ contains a physiologically active substance it does not follow that its physiological activity is due to that substance; for instance, we know that the thyroid contains arsenic in larger quantities than many other organs, yet nobody will claim that arsenic is the active principle of the thyroid, although arsenical preparations are all very active.

In 1899, Róos was the first to take exception to such views and reported the results of experiments tending to show there is a direct relation between the iodine content and the influence of the thyroid upon metabolism. He gave to a dog 5 mg. of children's desiccated thyroid containing 0.025 per cent of iodine. No effects upon the excretion of nitrogen nor upon the body weight were noticed. Another dose of 5 mg. of children's thyroid containing 0.18 per cent of iodine was found to cause an excretion of nitrogen of about 10 per cent; and as the same proportion of iodine contained in the thyroid increased, the effect upon the metabolism became proportionately more marked. Von Cyon and Oswald found that thyreoglobulin free of iodine obtained from goitrous calves had no effect upon the circulation, but became active in direct proportion to its iodine content. Marine and Williams in two experiments fed desiccated sheep thyroid containing different percentages of iodine to dogs and found that the loss of weight of the animal was in proportion to the quantity of iodine in the thyroid fed.

Des Ligneris demonstrated that iodine taken by mouth or given externally to young dogs causes in parenchymatous glands an increase of colloid, the folliculi become distended, the epithelium flattened, and the blood supply diminished. The same experiments made upon old dogs had very little or no effect at all upon the amount of colloid; in grown dogs with colloid glands iodine did not increase the amount of colloid.

Everybody knows Halsted's classical experiment: If a portion of thyroid is removed the remaining portion of the gland reacts by secondary hypertrophy, characterized by diminution or absence of the colloid

secretion, hyperplasia of the epithelium, and increased vascularization. But if, soon after partial thyroidectomy has been performed, iodine is administered to these animals no secondary hypertrophy takes place; if iodine is given previously and then only partial thyroidectomy is performed, very little or no hypertrophy takes place.

Marine and Lenhart not only confirmed these results but went a step further and claimed there is a constant relation between iodine content and the structure of the gland. They demonstrated that although it is true that in Halsted's experiments iodine will prevent compensatory hypertrophy, it will not have this effect if a maximum of thyroid is removed; compensatory hypertrophy will then take place just the same. In order to produce these changes the amount of iodine does not need to be very large; the smallest doses are very effective. The value of these experiments is quite doubtful, since we know that compensatory hypertrophy following partial resection of the thyroid must have been a mistaken observation. Halsted, in 1913, disproved his own findings in 1888 and Hunnicutt later confirmed Halsted's statements of 1913.

Marine and Lenhart believe (*loc. cit.*): "That the organism retains iodine in the same manner in which it retains iron and calcium. The difference between the maximum and minimum of iodine found to be compatible with the maintenance of the normal histological structure represents the excess of intake or consumption. If iodine falls below a quite constant level, the gland undergoes characteristic and constant histological changes, while if iodine is given these changes either do not occur, or if they have started they are arrested. It is of little or no consequence whether hyperplasia occurs in man or animal, or whether it is associated clinically with myxedema or exophthalmic goiter. In the presence of sufficient doses of iodine all true hyperplasia is prevented."

I do not know how far these conclusions are correct, but they certainly do not correspond to what we see in our daily practice. From the above statements we have the right to infer that glandular hyperplasia found in Graves's disease is due to a "more or less marked lack of iodine," that the severity of the disease is in direct proportion to the diminution or absence of iodine in the gland, and consequently that iodine treatment is the only logical treatment of the condition. Nothing has been less demonstrated than that "lack of iodine" is the cause of Basedow's disease, and that its severity is proportional to its presence or absence; on the other hand, nothing has been better demonstrated than that iodine is not the specific treatment of exophthalmic goiter. More so, in the great majority of cases it is harmful. Furthermore, we know now that Halsted's compensatory hypertrophy does not exist.



Although variable in its limits the highest iodine content per gram is found in normal glands. Whether these variations are due to variations in the intake or in the consumption within the organism or to both is not known. More probably they depend upon the intensity of the chemicobiological metabolism whose intensity varies with each given individual.

In parenchymatous and exophthalmic goiter the amount of iodine usually varies inversely with the degree of glandular hyperplasia; consequently, the lowest amount of iodine will be found with the highest degree of hyperplasia. Yet Oswald, Caro, Smith and Broders, myself and others have observed cases of Graves's disease in which thyroid hyperplasia and the iodine content were remarkably high. As in marked hyperplastic conditions colloid is generally absent or very much diminished, it might be permissible to say that iodine varies in direct proportion to the amount of stainable colloid. Aesbacher strengthened these views by finding a diminished iodine content in alcoholic intoxication and in acute inflammatory diseases of the thyroid. This was to be expected, as we shall see in the chapter on Bacterial and Toxic Thyroiditis, that in such conditions there existed at the same time a glandular hyperplasia and a diminution of colloid.

Claude and Blanchetiere, however, refuse to see any such parallelism between colloid and iodine, as they have found high iodine content in glands where no colloid was present. Using Mallory's connective-tissue stain as an indicator of iodine, or of its organic complex present in the colloid of the thyroid, Tatum, in 1916, was unable to find any certain relation of iodine content of thyroid glands and the capability of reacting with either orange A or aniline blue. The reason may be that, in Tatum's judgment, Mallory's connective-tissue stain is not an indicator of the presence or absence of organic iodine, as reported by Jones in 1913. As De Ligneris, Tatum also noticed that animals fed on thyroid extract or on potassium iodide showed an increased amount of colloid.

It is very well agreed that colloid glands in general contain less iodine than normal glands, although to this there are many exceptions, as shown by Oswald. In fetal adenoma Marine and Williams found iodine, and there, too, the iodine content was in direct proportion to the glandular hyperplasia. The total amount of iodine that a gland may contain depends upon its size, the diet, locality, medication, etc. As regards the iodine content in human thyroids of cretins no specific observations are recorded, but as these glands are atrophied we can assume that the iodine content must be low. In old age there is a slight decrease of iodine seemingly proportionate to the degree of senile atrophy.

Be that as it may, the fact becomes more and more evident that

iodine must not be regarded as purely accidental, but that it plays some important function in metabolism. The merits of having come nearer the solution of this problem certainly belong to Reid Hunt and Atherton Seidell. In extremely elegant and conclusive experiments they demonstrated that if small amounts of thyroid are fed to mice for a few days these animals acquire a markedly increased resistance to acetonitrile. Thus, a mouse which had been fed with thyroid for nine or ten days recovered from seventeen times the relative amount of acetonitrile fatal to the controls; hence the conclusion that thyroid enables the mouse to "neutralize" or resist in some way doses of acetonitrile which in ordinary conditions are fatal. From another series of experiments it was found that if 1 part of iodothyryn was fed to a mouse for ten days, it enabled the mouse to resist more than 240 times an equal amount of acetonitrile.

Up to that time iodine-free thyroids were regarded as being deprived of their physiological activity. With their delicate tests the same authors were able to demonstrate that this is not the case. They found that iodine-free thyroids have a low degree of physiological activity, that their activity is lower than the thyroids containing iodine, and that their physiological properties increase in direct proportion to the amount of iodine. Consequently, it may be concluded that the activity of iodine-free thyroids is nevertheless largely due to the iodine present in too small quantities to be detected, or that the iodine-free thyroglobulin has of itself some physiological properties. The latter possibility would explain why in Hunt's and Seidell's experiments certain iodine-free thyroids were more active than thyroids containing small amounts of iodine. It may be supposed that iodine-free or iodine-poor thyroids can meet the ordinary demands of the organism; but if the demands upon the thyroid are not adequate to the function of the iodine-free gland, marked symptoms of hypothyroidism will follow, as shown, for example, by the losses suffered by sheep breeders on account of cretin lambs before the extensive use of iodine-containing salt.

Continuing their experiments, Hunt and Seidell found that the resistance of rats, mice and guinea-pigs to morphine is uniformly lowered after thyroid feeding. In the case of rats there is a close parallelism between the physiological effect of the thyroid as determined by the increased susceptibility to morphine and the percentage of iodine. A similar parallelism was found in general in experiments on mice. Animals which had received thyroid with a higher percentage of iodine showed a better resistance. There is no explanation for the cause of this increased susceptibility.

Marine, in 1916, sought to determine whether the thyroid cells exhibit a special affinity for iodine or not. The thyroid gland, spleen and

kidney were separately perfused both *in vivo* and *in vitro* with Ringer's solution containing KI. He came to the following conclusion: "Artificially perfused thyroids take up and retain KI to the same extent as do *vivo*-perfused thyroids. KI is not absorbed by the cells of the spleen, liver, kidney or muscles. The amount of KI absorbed by the thyroid is not independent of the concentration of KI in the perfusate. Only surviving glands exhibit the ability to take up the KI. KCN inhibits this activity. Small amounts of iodothyreoglobulin wash out during perfusion with defibrinated blood. Autolyzing glands do not take up KI but give that which was previously stored. The KI stored in surviving cells is pharmacologically inactive."

When frozen section preparations of unfixed thyroid glands are floated in isotonic salt solution the colloid separates out. Using this phenomenon as a basis of procedure, Tatum prepared large amounts of sectioned material from relatively fresh beef, sheep and pig thyroid glands, extracting them with Ringer's solution and submitting them to centrifugation. This was repeated and iodine determinations were made on the residual cell bodies, the whole glands and the extracts. There appeared to be a wide variation in the absolute amounts of the total iodine in the whole glands and in the cell masses. Nevertheless, the ratio of the percentage of iodine in the cells to the percentage of iodine in a whole gland was found to be a clearly constant value, and was considerably less than 40 per cent. From these results it is evident that iodine exists in both the cells and the colloid of beef, sheep and pig thyroid glands.

Swingle, in 1919, observed that iodine and its compounds, fed to frog and toad larvæ, stimulate metamorphosis very rapidly. He found, furthermore, that inorganic iodine fed to thyroidless larvæ of toads caused a very rapid metamorphosis, despite the fact of complete absence of thyroid in them. Hence, his suggestion that iodine might be regarded as a hormone in itself, capable of functioning without the aid of the thyroid. How far we are justified in transferring these results obtained in this low scale of the animal kingdom to the one at the top of the scale, man, remains to be seen.

If we sum up the results of all the experiments mentioned and weigh them, it cannot be denied that a fact stands forth most strikingly, namely, that iodine seems to be of great importance in the thyroid's physiological activity. This is so true that Oswald considers iodothyreoglobulin as the active principle of the secretion, because, according to him, it possesses all the physiological properties of the thyroid. As we know, one of the most important properties of the gland is to cure spontaneous as well as operative myxedema. Now, then, Oswald treated a young myxedematous boy, eighteen years old, measuring 131 cm. in



length. He gave the boy a daily dose of 0.1 gm. of iodothyreoglobulin for twenty-one months. During that period of treatment the patient grew 21 cm., lost his cretinoid appearance and improved in every respect, mentally as well as physically. Pick and Pineles have come to the same conclusions experimentally.

Another property of the thyroid is to increase oxidation of fat and albumin. This property is found, too, in iodothyreoglobulin. Thyroid extract increases the susceptibility of the vagus fibers to the faradic current; iodothyreoglobulin does the same. According to Oswald no other substance in the thyroid has a single one of the same properties as the iodothyreoglobulin, and these properties are due to the iodine combined with a globulino-albuminoid substance.

Is it really so? Is it really to iodine that thyreoglobulin owes its physiological properties and is iodothyreoglobulin the true active principle of the gland? Baumann and Hutchinson, Oswald, Gauthier and others say "Yes," whereas Fraenkel, Dreschel, Gottlieb, Chassavant, Hunt, Seidell, etc., claim that the iodized proteids are not the only ones possessing physiological activity. Most probably each group holds a part of the truth; neither one of the compounds can be considered as representing the whole active principle of the thyroid gland; there must be other compounds endowed, too, with some physiological properties. This is suggested by the fact that every kind of thyroid preparation, and they are numerous, has some of the physiological properties of the thyroid, and that the thyroid *in toto* given as medication has succeeded where iodized preparations have failed.

The nearest approach to the isolation of the active principle of the thyroid has been made by Kendall. Since it embodies best all the physiological properties of the thyroid, time will probably show that thyroxin must be regarded as the *active principle* of the thyroid. It contains 60 per cent of iodine. That many compounds up to this time, because of their physiological properties, have been considered as representing the active principle of the thyroid, must very likely be due to the fact that they all contain thyroxin.

If iodine plays an important part in the clinical function of the thyroid secretion, we must not forget that there are in the thyroid other chemical compounds to which not enough consideration has been given. *Arsenic*, for example, as previously said, exists constantly in the thyroid, and is present in that gland in quantities larger than in any other organ of the body. Certainly, its presence is not an accidental one; it must play a part in the physiological activity of the gland. In nature arsenic and iodine do not exclude each other; on the contrary, they are most frequently found associated; sulphurous and iodized waters contain arsenic; algæ, for instance, contain iodine and arsenic always

mixed together. Furthermore, iodine combined with arsenic is always an excellent thyroid medication. According to A. Gauthier, arsenic is found in the thymus, skin, brain and hypophysis, but nowhere else. Is this only a coincidence, or has it a greater significance than it seems to have at first? The answer is not yet at hand, but it will be interesting to note that the thymus, brain, skin and hypophysis are precisely the organs electively involved in thyroid disturbances.

*Phosphorus* is constantly present in the thyroid. According to Bayer, 5 gm. of fresh thyroid contains 0.00102 gm. of  $P_2O_5$  (pentoxide of phosphorus). Kocher regards phosphorus as playing an important part in thyroid physiology. There seems to exist an antagonistic action between iodine and phosphorus.

Brisson, who has investigated the sulphur content of several endocrine glands, found 0.23 gm. of baryta sulphide per 2 gm. of thyroid. The organs which contain the greatest quantity of sulphur are the suprarenal bodies, testicles and keratine.

In the thyroid Iscovesco found *lipoids*, which possess a very energetic physiological action. According to him there is in the organs of vertebrates a specific and unique lipoid which, injected into the organism of an animal, has the property of localizing its action on the organ from which it originates and on this one only. These lipoids are called *homostimulants* because they exert their action by an elective influence on the medullar centers controlling the organ from which they derive. One of these lipoids, called by Iscovesco *thyrol A*, injected hypodermically produces exophthalmos, tachycardia, and swelling of the thyroid; another lipoid when given in doses of 2 cgm. per kilogram produces cachexia.

The activity of the gland was thought to depend upon its ferments, and lately Youchtchenko showed that the thyroid secretion contains a great quantity of *catalases* and *peroxydases*. These ferments preside over the oxygen exchanges in the organism. In carnivorous animals he found in the thyroid a certain amount of *lipases*, a ferment which intervenes in the metabolism of fat. This would explain certain conditions found in hypo- and hyperthyroidism. In hypothyroidism the peroxydasic and lipasic ferments, being diminished on account of the reduced function of the thyroid, oxydative processes will be diminished, hence the sensation of cold, adipositas, etc.; on the other hand, in exophthalmic goiter, the cellular activity being increased, the ferments are in greater quantity; consequently the metabolism is accelerated; hence the sensation of heat, elevated bodily temperature, loss of flesh, etc.

In summing up we see that the pharmacodynamic function of the thyroid, as of other organs, the liver, for instance, is not one but is multiple; it seems therefore logical to ascribe to the thyroid several

functions: an *iodine function* presiding over the general metabolism; a *phosphorous function* presiding over the thermogenesis and over the vasomotory system regulating the cardiac rhythm; a *sulphurous function* presiding over the nutrition of the skin and the pileus system; and an *arsenical function* presiding over the nervous function and whose insufficiency causes, according to Hertoghe, migraine. Most likely every one of these functions takes place through a special hormone.

Of all the chemical work on the thyroid to date, Kendall, in isolating the crystalline substance, thyroxin, having a definite chemical formula, the physiological action of which is the same as that of the gland itself, has apparently furnished the most satisfactory results.

**Conclusions Concerning the Thyroid Function and its Chemistry.**—The thyroid is an organ necessary to life and plays an important part in metabolism. It presides over the nutritional exchanges, over the osseous growth, and regulates the nervous and vascular systems. Its insufficiency causes *hypothyroidism*. To this condition belong not only myxedema and cretinism, but also a large series of intermediate borderline stages called by Hertoghe “form frustes,” and characterized, as we shall see later, by disturbances in the sexual apparatus, gastro-intestinal tract, osseous system, etc. These disturbances may be more or less marked; many of them may be present at the same time, or there may be only one symptom to betray a slight degree of thyroid insufficiency.

Thyroid and parathyroids differ not only embryologically and anatomically, but are also functionally two different organs. Complete removal of the thyroid gland produces chronic nutritional disturbances, as retarded osseous growth, myxedematous infiltration of the skin, marked reduction in general metabolism with profound psychic disturbances. On the other hand, complete parathyroidectomy causes acute nervous conditions, as convulsions, tetany, which soon terminate in death. At the same time, hyperthermia, tachycardia and dyspnea, as found in acute intoxications, are present.

What is the active principle of the gland? We may say that most likely this active principle is not one but is multiple. Up to 1914 the one which we knew best was *iodothyreoglobulin*. It was regarded by many as the real and only active principle of the thyroid. The last to date is the *thyroxin* of Kendall. It has a definite chemical formula and is regarded by its discoverer and by Plummer as the active principle of the thyroid. Judging by the clinical results obtained by Plummer in the treatment of hypothyroid patients with thyroxin, and judging, too, by my experience with that drug, there is no doubt that thyroxin is strongly active, and that most likely it constitutes *the* or *one of the most important active principles of the thyroid*. No doubt it plays a very important part in metabolism and controls to a great extent the growth



of the osseous system; better than any other, this substance embodies the physiological action of the thyroid itself.

But most likely it is not the only one; there are other substances in the thyroid which are physiologically important; there is a *phosphorous* principle probably presiding over the vasomotory system regulating the cardiac rhythm and thermogenesis. We have also seen that there is a *sulphurous* principle presiding particularly over the nutrition of the skin and pileus system. Finally, there likely is, too, an *arsenical* principle which has a certain action over the nervous system. Every one of these principles represents, we may say, a special *hormone*.

How these different hormones, and very likely others which we have not yet discovered, exert their action and where is not known. Shall we consider them as excitants of the cellular nutrition facilitating the assimilative process, or shall we consider them as substances necessary to the cell itself and its functions, just as traces of zinc seem to be an absolutely necessary aliment for the *aspergillus niger*? The answer is still not at hand.

Biedl thinks that there are in the thyroid two hormones which he calls *dissimilatory* and *assimilatory*. According to him the dissimilatory hormones activate the normal activity of the organs, of the heart, of metabolism, of the adrenals, of hypophysis, etc. The assimilatory hormones, on the contrary, paralyze a great many organs and functions, as the growth of bones, the function of the pancreas, etc.

The fact that thyroid substances resist the action of the stomachal and intestinal digestive ferments shows that its main active principle is more than an albuminous substance. Certainly, it is difficult to admit that the ferments as catalases, peroxydases and lipases found in the thyroid have no pathological significance and that their presence in that organ is purely accidental. These ferments preside over the oxygen exchanges and intervene in the metabolism of fat. The same may be asserted for the *lipoids*; they certainly must play some part in the very complicated biological chemistry of the thyroid. Consequently, we are led to believe that the thyroid function is not *one* but is *multiple*—at any rate it is an extremely important one.

**Detoxication.**—How does this gland exert its influence over the metabolism? A great majority of authors believe that the gland has a *detoxicating action* and that it secretes substances which neutralize poisons resulting from metabolism. This was the opinion of Schiff and seems to be corroborated by the fact that intense bleeding in thyroidec-tomized animals diminishes the intensity of hypothyroidism symptoms. Intravenous injection of salt solution does the same thing. It might consequently be inferred that toxic products have been partly eliminated with the bleeding or dissolved by the physiological solution injected.



Notkine believes that the *thyreoproteid* is the toxin which is the real cause of myxedema, and that the physiological action of the thyroid consists in neutralizing the thyreoproteid contained in the organism. Fraenkel believes that the neutralizing agent is the *thyro-antitoxin*, Baumann thinks that it is the *iodothyrim*, and Oswald the *iodothyreoglobulin*. Von Cyon believes that the principal function of the thyroid is to transform *iodine compounds* into a harmless organic combination, the *iodothyrim*; Blum, that the thyroid neutralizes in the gland itself the toxic products of intestinal origin, the *enterotoxins*. According to him there is in the thyroid an intermediary product which he calls *thyrotoxalbumin*, whose antitoxic power is due to iodine. As it is possible to obtain from the thyroid various albuminous bodies with a varying iodine content, Blum believes that bodies poor in iodine are the more poisonous, that the ones containing the most iodine are non-poisonous and non-toxic, and that the ones saturated with iodine are harmless. On the nature and quantity of these various by-products reaching the circulation depend the various clinical conditions, as tetany, cachexia, etc. Blum does not make a difference between the thyroid and the parathyroids; he considers the latter glands as the younger forms of the thyroid. According to him iodine never leaves the thyroid to go into the organism, which statement he thought he proved by feeding dogs with an iodine-free diet for months; yet at the end of that time he was still able to find iodine in the thyroid. Cachexia, myxedema and tetany are the results of an antithyreotoxin, the thyroid being unable to neutralize such products. Dor claims that iodine is transformed into an organic combination which in the general metabolism plays the role of a *ferment*. Kishi believes that the thyroid neutralizes the toxic products of metabolism, especially the ones of muscular origin, and that it destroys the *nucleoproteids*, which are of cellular origin, and which are introduced into the organism with the food. When neutralized, these toxic substances are eliminated later on through the kidneys.

Where does this detoxication take place? Does it take place in the thyroid or outside? Shall we consider this gland as a great chemical laboratory where the most important and most delicate reactions take place? Or shall we consider it as a filter, a sort of "clearing-house," where everything is carefully revised? As the thyroid is a glandular organ and not a lymphoid one it is difficult to accept the opinion that the detoxicating action takes place in the thyroid itself. On the other hand, the fact that thyroid given by mouth, rectum or any other way is physiologically active shows that most probably the thyroid secretion exerts its action outside of the gland.

This detoxicating theory, however, is not entirely satisfactory.

Farrant, in 1913, after experimenting on horses and guinea-pigs

came to the following conclusions: Certain diseases, and especially certain toxemias, cause hyperplasia of the thyroid gland in man and in animals. Among these, diphtheria toxin has been examined especially, and it has been found that a small dose is sufficient to elicit hyperplasia in a susceptible animal, but that as immunity is acquired the thyroid no longer undergoes hyperplasia under the toxin. The hyperplasia thus decreases as the antitoxic value of the serum increases. The thyroid gland, in other words, is protected from the action of the toxin by the presence of antitoxin in the serum. There is no reason to suppose that any special relation exists between antitoxin formation and the thyroid gland; the latter is not antitoxic itself.

Bassinger, in 1917, injected minimal, subminimal, and repeated subminimal lethal doses of diphtheria toxin into the thyroid of a dog. In a second series he used tetanus toxin. He came to the conclusion that the thyroid has no detoxicating effect that can be demonstrated.

Lindemann, studying the effects of caffeine when injected into the carotid artery of thyroidectomized animals, found that the dose necessary to kill a dog so treated was ten times larger than the one necessary to kill the control. We have seen that R. Hunt and A. Seidell found that mice which had been fed with thyroid for eight or nine days before were able to stand a dose of acetonitrile ten to twenty times larger than the one necessary to kill the control.

How to explain these results? Of course the partisans of the "detoxicating theory" will claim that acetonitrile was neutralized and consequently rendered harmless, but Hunt and Seidell do not share the same view and believe that the function of the thyroid in such cases prevented the formation of the poison from nitrile because they found that the thyroid had no effect upon the toxicity of hydrocyanic acid itself, which is the poison resulting from decomposition of acetonitrile. They deem it impossible to think of any way in which such neutralization could occur, as the amounts of acetonitrile rendered harmless are so out of proportion with the amounts of thyroid fed. In their judgment the thyroid seems to alter the metabolism in such a way that the acetonitrile is disposed of without breaking down into its poisonous constituents, as occurs in normal glands.

To believe that acetonitrile rendered harmless is out of proportion to the amounts of thyroid fed is no argument against the neutralization theory. Most probably the thyroid hormones do not differ from those of other organs. We know, for instance, that extremely small amounts of adrenalin are capable of causing the most energetic and powerful muscular contractions, the effect in this case being entirely out of proportion to the cause. We know, too, that very small amounts of secretin are capable of causing an abundant pancreatic and duodenal secre-

tion; that all *diastases* contain a metal or metalloid in absolutely imponderable proportions, yet absolutely necessary for their efficacy, though entirely out of proportion to their effects. To be sure, arguments are not facts, and so there is still room for discussion.

Were there a direct interaction between poisons and the thyroid, the same results should be expected in all classes of animals. Hunt and Seidell have shown that if the thyroid protects mice against acetonitrile, on the other hand it increases the susceptibility to these poisons in rats and guinea-pigs. If, then, the thyroid has a neutralizing action, why should it neutralize in the one case and not in the other? Therefore, these authors conclude that when an unusual poison, such as acetonitrile, is introduced into an animal its fate will depend upon how the animal's metabolism concerning this poison has been affected by the thyroid. The metabolism of mice has been affected in such a way that acetonitrile is rendered harmless, whereas in rats and guinea-pigs it becomes harmful. What occurs to acetonitrile is compared by Hunt and Seidell to what happens to methyl and ethyl alcohol (*loc. cit.*): "When such a poison as ethyl alcohol is introduced into the organism, the metabolism not only renders it harmless but makes it useful for the body in utilizing the energy set free. In the case of methyl alcohol, although oxidation may proceed along similar lines, part of the alcohol is converted into poisonous substances (formaldehyde and formic acid). The fate of acetonitrile in the body of the mouse must be compared to the fate of ethyl alcohol, and the fate of acetonitrile in the body of the rat which has been fed with thyroid to that of methyl alcohol." Consequently, these authors and others, as G. Gauthier, believe that the thyroid gland instead of neutralizing the toxic products of metabolism prevents their formation. It has, then, a *regulating action* on the nutritional exchanges.

Kendall believes that the function of the thyroid is to furnish the organism with ammonia resulting from the deaminization of amino-acids; that the amino group in the amino-acids is available for the formation of urea and other nitrogenous compounds only when split from the amino-acids, and that, consequently, deaminization seems to be the function of the thyroid.

In conclusion, we must regard the thyroid as one of the most powerful activators of metabolism. This takes place through the iodine-containing hormone, the *thyroxin*, and most likely through other principles of lesser importance. If the work of Asher and Flack and of Cannon and his co-workers is confirmed, then the influence of epinephrin is very important in augmenting its action, and *vice versa* the thyroid greatly increases the pressor activity of epinephrine.

Bram's figurative way of speaking possibly best conveys what is

meant by the activating properties of the thyroid when he says: "To make a simple analogy, it can therefore be concluded that the effect of thyroid secretion on metabolism is somewhat similar to the relation of fuel to a furnace. A *normal* amount of thyroid substance within the tissues keeps them in a state of poise or equanimity, *i. e.*, in an equilibrium between destructive and constructive forces whereby the individual is said to be normal in structure and function of body and mind. A *diminution* of this secretion keeps the furnace low, and we have a diminished 'burning down' of material plus the lessened elimination of waste matter through the blocking of the 'draught,' because of lowered function of the excretory organs; thus the patient's physical and mental activity is somewhere between normality and zero, depending on the degree of the affection. An *increased* quantity of thyroid secretion creates a state of extreme 'firing' of the bodily furnace; the balance between anabolism and katabolism is broken in favor of the tremendous increase of oxidation of body tissues which 'burn down'; during the process there is a marked quickening of all eliminative functions, with the result that the patient becomes almost a shadow of his former self."

**Functional Interrelation of the Organs of Internal Secretion.**—It would be a mistake to believe that the thyroid is left entirely to its own resources in its gigantic task, the regulation of the metabolism. It is in direct interrelation with the other organs of internal secretion. (See page 442-448.)

It will be seen that there is between all the organs with an internal secretion a functional correlation, a sort of *physiological teamwork*. The normal function of one organ is dependent to a certain extent upon the normal function of the others, and when one is out of order it cannot fail to have a pathological repercussion on the others. Endocrinology is a science still in its infancy, but its promises are far-reaching; if fulfilled it will be one of the richest fields to harvest.



## CHAPTER IV.

### PATHOLOGY.

*Synonyms in Latin:* Struma; guttur turgidum; Guttur-throat. *French:* Goitre; gros cou. *German:* Kropf; Blæhals. *Italian:* Gozzo. *Spanish:* Papera. *English:* Goiter; great neck; Derbyshire neck.

According to Virchow a goiter is only the continuation of the natural development of the thyroid gland. In a follicle, cellular proliferation takes place by division of the cells, which gradually form solid papillary formations bulging in the interior of the follicle and filling the follicular lumen. Interstitial connective tissue penetrates these papillary formations, carrying with it their vascular supply. Gradually they shape themselves into a more or less follicular form. In this, colloid secretion appears; hence the follicle; hence the goiter.

If this process is localized to a part of the gland, then we have a *nodular goiter*; but if this process takes place all over the gland, then we have a *diffuse goiter*. Such goiter may become later on a cystic, fibrous or a calcareous goiter; this depends, however, upon the secondary degenerative changes which will take place in it. In conclusion, according to Virchow, a goiter originates by the subdivision of adult folliculi into smaller ones; these in turn proliferate and finally form other adult alveoli. Hitzig, in 1894, shared the same view.

In 1893, Wölfler modified Virchow's conception as to the origin of goiter. Contrary to Virchow's theory, which claims that goiter is due to *hyperplasia*, Wölfler claims that it is due to *neoplasia*; that it is the consequence of the proliferation of the embryonic epithelium, remaining between adult alveoli, and which is found mostly in the cortical zone of the gland. These embryonic cellular residues, according to Wölfler's theory, are the ones which at one time or another may begin to proliferate and form goiter, which Wölfler calls *adenoma*.

In his judgment an adenoma is an epithelial tumor with atypical vascularization, developed from embryonic glandular residues. If in the proliferating process the epithelium keeps its embryological aspect, the consequence of it is a *fetal adenoma*; but if the epithelium tends gradually toward the adult aspect, it then gives rise to a *parenchymatous* and *colloid goiter*. Wölfler distinguishes two kinds of adenoma, the *benign* and *malignant*.

These two theories, although extremely interesting and partly cor-



rect, do not explain satisfactorily the origin of all the tumors found in the thyroid gland; for instance, they do not explain the origin of goiters with squamous epithelium, and they do not take into consideration at all a number of tumors found in the thyroid gland which have, as we shall see later on, a very different origin. I refer to tumors developed from the thyroglossal duct; from the parathyroid; from the postbranchial bodies, etc.

In the last few years the study of the embryology of the thyroid has afforded more light on the obscure field of its pathology. This has been true, too, of the ovary, testicle and kidney. We might say there is a peculiar analogy between tumors developed in these organs and those developed in the thyroid. Tumors developed in the parathyroid and called *parastruma* are analogous to renal tumors called *hypernephroma*, and which are developed from the suprarenal bodies. Tumors with cylindrical epithelium originating from the thyroglossal duct find their analogy in tumors developed in *Wolf's canal*. Mixed tumors of the thyroid originating from the branchial bodies find their analogy in the mixed tumors of the kidney originating from the primitive scleromyotomata. Langhans, of Berne, and his pupils, Michaud, Verebely and Getzowa, are entitled to a great deal of credit for attempting to clear up this question of the origin of thyroid tumors. Lately, De Quervain, in 1909, and Berard and Alamartine, in 1912, took up this subject, looking at it from an embryological point of view.

We call goiter any enlargement of the thyroid gland. If this enlargement shows clinically and pathologically the characteristics which we attribute to benign tumors, then it is called *benign goiter*; otherwise we call it *malignant goiter*. If vascular symptoms and congestion are the predominating features, then we regard it as a *vascular goiter*. If infection sets in in a preëxisting goiter, we call it *strumitis*; but if infection affects a normal thyroid, we call it *thyroiditis*.

The enlargement may affect only a part of the gland or the gland *in toto*. If the goiter is made up of one or several nodules, we call it *nodular goiter*. If the enlargement is diffusely distributed throughout the gland, we call it *diffuse goiter*. We may have a diffuse parenchymatous goiter or a diffuse colloid goiter, according to the nature of the thyroid degeneration.

In nodular goiter proliferation and the distribution of follicles are very much more irregular and unequal. The nodular goiter is usually colloid or cystic and has a greater tendency to undergo hyaline, fibrous, or calcareous metamorphosis. Hemorrhage takes place more frequently in nodular than in diffuse goiter. The nodular goiter is more common in the lower pole of the gland. It is oftentimes multiple and seldom develops in the pyramidal process.

A satisfactory *clinical* classification of the thyroid tumors is not easy on account of the difficulty of bringing into harmony the clinical with the pathological facts. The classification based on embryology alone is extremely interesting and scientific, but clinically it is confusing, as it mixes up in the same chapter the benign and malignant forms of goiter, which, clinically, are so different. Therefore, I think that until we have something better the following classification will answer the purpose:

## BENIGN TUMORS.

- |                           |   |                                 |              |
|---------------------------|---|---------------------------------|--------------|
| I. Parenchymatous goiter. | { | 1. Physiological                | { Puberty.   |
|                           |   | 2. Non-toxic.                   | { Pregnancy. |
|                           |   | 3. Thyrotoxic.                  |              |
| II. Colloid.              | { | Cystic.                         |              |
|                           |   | Fibrous.                        |              |
|                           |   | Calcareous.                     |              |
|                           |   | Osseous.                        |              |
| III. Fetal adenoma.       |   |                                 |              |
| IV. Accessory goiters.    | { | Median cysts.                   |              |
|                           |   | Lingual goiter.                 |              |
|                           |   | Intratracheal goiter.           |              |
|                           |   | Intrathoracic accessory goiter. |              |
|                           |   | Ovarian goiter.                 |              |

## MALIGNANT TUMORS.

- |                               |   |   |
|-------------------------------|---|---|
| I. Epithelial tumors.         | { | 1. Malignant adenoma or proliferating goiter. |
|                               |   | 2. Carcinoma.                                 |
|                               |   | 3. Metastatic colloid goiter.                 |
|                               |   | 4. Parastruma.                                |
|                               |   | 5. Postbranchial goiter.                      |
|                               |   | 6. Papilloma.                                 |
|                               |   | 7. Cancroid.                                  |
| II. Connective-tissue tumors. | { | 1. Fibrosarcoma.                              |
|                               |   | 2. Polymorphous-cell sarcoma.                 |
|                               |   | 3. Round-cell sarcoma.                        |
|                               |   | 4. Myxosarcoma.                               |
|                               |   | 5. Endothelioma.                              |
|                               |   | 6. Perithelioma.                              |
| III. Mixed tumors.            |   |   |
| IV. Dermoids, Teratoma.       |   |   |

## INFLAMMATIONS.

- |                   |   |                     |                      |
|-------------------|---|---------------------|----------------------|
| I. Bacterial.     | { | Acute               | { Non-purulent.      |
|                   |   |                     | { Purulent.          |
|                   |   |                     | { Syphilis.          |
|                   |   | Chronic             | { Tuberculosis.      |
|                   |   |                     | { Woody thyroiditis. |
| II. Toxic.        |   |                     |                      |
| III. Parasitical. | { | Chagas thyroiditis. |                      |
|                   |   | Echinococcus.       |                      |

## BENIGN TUMORS.

**Parenchymatous Goiter.**—This type of goiter is formed by glandular proliferation. It is associated with metabolic disturbances, with puberty, menstruation, pregnancy, lactation and the menopause. Nothing is known definitely regarding the cause of thyroid hyperplasia at these periods.

Diffuse enlargement of the thyroid gland, non-toxic in nature, is often observed. It is then known as the *non-toxic parenchymatous goiter* (Fig. 9). When toxic symptoms are present we call it *thyrotoxic parenchymatous goiter*. This latter form will be studied in the chapter on Exophthalmic Goiter.

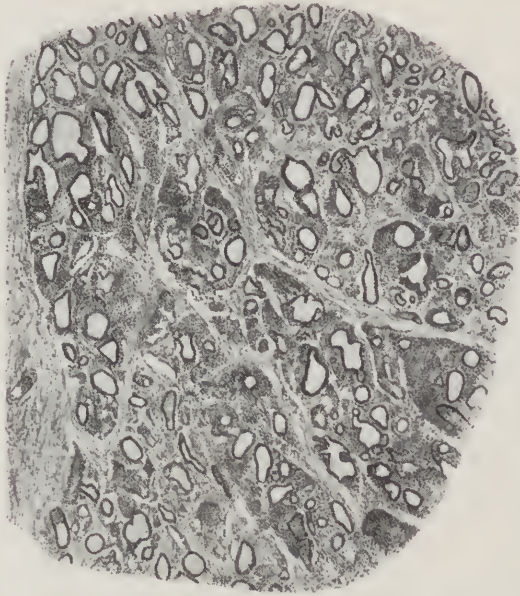
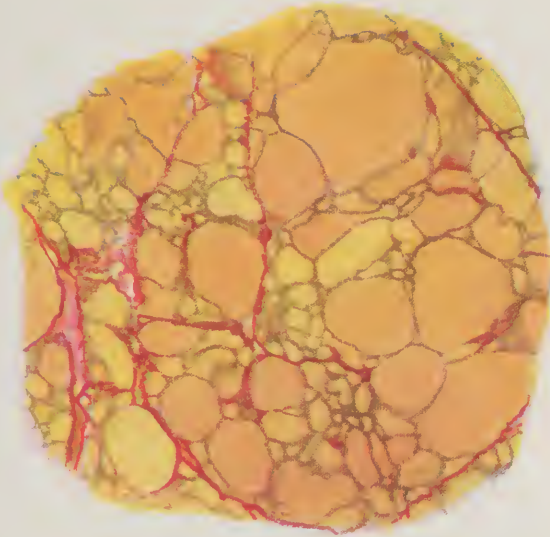


FIG. 9.—Non-toxic parenchymatous goiter.  $\times 53$ .

Histologically, the physiological and non-toxic parenchymatous goiter is characterized by an enlargement of all the glandular elements. The follicles are increased not only in number but also in size. They may contain colloid in slightly larger quantities than normally, or they may not. The colloid is rich in iodine. The number of cells shows an increase in size and number also. The interfollicular connective tissue may be normally developed or slightly increased. The cut surface of the gland is slightly granular as the consequence of the increase in the size of the follicles and their bulging out. Its consistency is firm. Iodine generally has a marked therapeutic effect on this form of goiter.

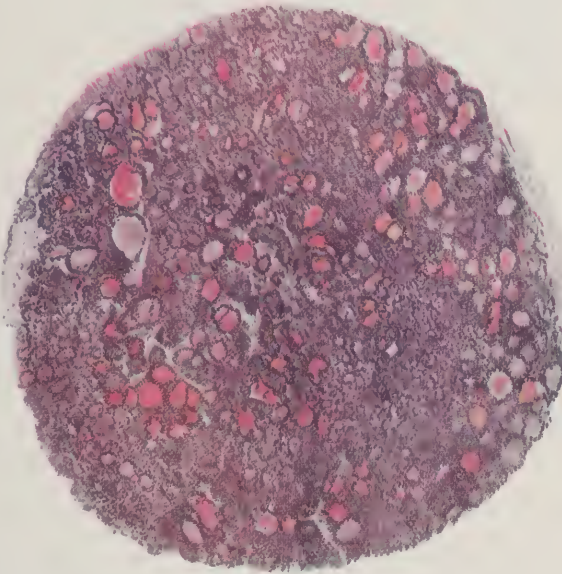
# PLATE I

FIG. 1



Colloid Goiter.  $\times 40$ .

FIG. 2



Wölfer's Fetal Adenoma.  $\times 100$   
With intrafollicular hemorrhages.





The histological picture of the goiter taken altogether is a picture of a more or less normal gland in which all the elements show an increase in size and number, but in which the different elements have kept more or less their natural relations, one to another.

**Colloid Goiter.**—Its main characteristic is the increased quantity of colloid. This colloid is generally thick, staining readily. It contains fewer vacuoles than normally and completely fills the follicle. Its iodine content is diminished.

The follicles have lost their normal proportions and show all kinds of form and size. (Plate I, Fig. 1.) The epithelium is low or flat; the blood supply of the colloid goiter is diminished, and the interfollicular stroma is more or less abundant, showing, as a rule, extensive hyaline degeneration (Fig. 10).

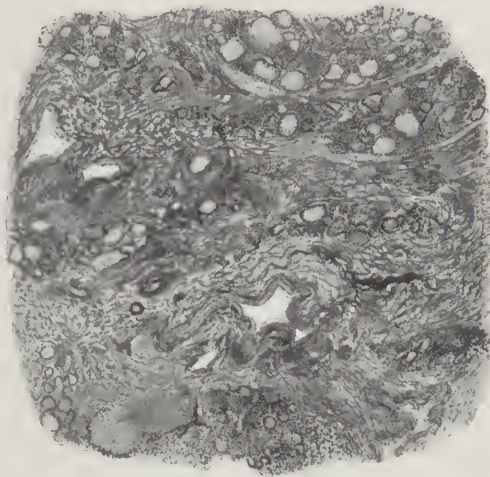


FIG. 10.—Hyaline degeneration and increased connective tissue of a goiter. First step toward formation of a fibrous goiter.  $\times 40$ .

If the colloid degeneration does not affect the diffuse type, but is nodular, the surface of the goiter is then coarsely lobulated. The consistency may be harder or softer than in parenchymatous goiter, and the cut surface, more or less irregularly lobulated, shows a thick, tenacious, transparent material which is colloid. Its color depends upon its content of hemorrhagic blood.

It would be erroneous to believe that even in a diffuse colloid goiter every follicle has undergone colloid degeneration. Between the degenerated follicles there is always a number of normal vesicles and non-differentiated cellular masses of embryonic type, which will proliferate and form new alveoli in order to take up the lost or diminished function of the degenerated follicles.

Colloid degeneration may affect the entire gland and give rise to a *diffuse colloid goiter*, or, localized to a small portion of the thyroid, may form a *nodular colloid goiter*. Colloid nodules may be singles or multiples.

The colloid goiter may give rise to a *cyst*. There are two kinds of cyst, the *true* and the *false*.

The *true cyst* is of follicular origin. Two or more follicles become distended by the colloid secretion, and as a consequence of the continued eccentric pressure on their follicular walls the blood supply is slowly cut off, the alveolar walls undergo atrophy, and finally break and fuse together, forming a larger space filled with colloid (Fig. 11). The cyst

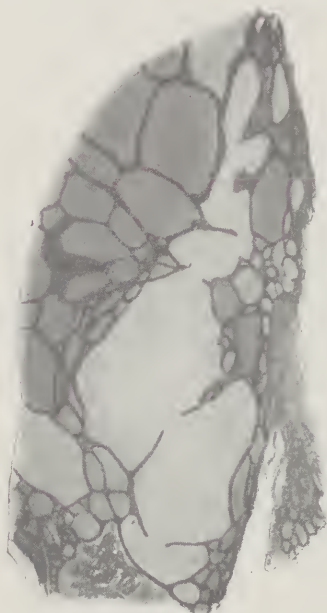


FIG. 11.—Walls between large colloid alveoli become atrophied and give rise to a cystic formation.  $\times 21$ .

is formed. It increases gradually in size, assumes a round form and presses toward the periphery the surrounding follicles, which, owing to the continuous pressure, undergo a connective-tissue degeneration and fuse with the true or follicular capsule of the cyst, thus forming a thick capsule. A cyst may, furthermore, take its origin from an intrafollicular hemorrhage.

The *false cyst* is the consequence of a hemorrhage which dissociates the stroma of the gland and causes a necrotic, aseptic area. If the hemorrhage is of small size it gradually becomes absorbed. Pigmentation remains for a long time as the only proof of the bloody extravasation. But if the hemorrhage is of some consequence, the hemorrhagic focus being too large to become absorbed, a localized, aseptic necrosis takes place and the neighboring tissues begin to proliferate, forming a false capsule around this hemorrhage; hence the formation of an encapsulated cyst.

The size of a true cyst may become enormous. As the ovarian cyst it may be mono- or multilocular and may contain a serous, transparent fluid, which may be red if a recent hemorrhage has taken place, or it may be of chocolate-brown color if the hemorrhage is older. The hemorrhage is the result of a rupture of one or more small bloodvessels of the wall of the cyst, as a consequence of the chronic endarteritis, or of atrophic changes resulting from mechanical pressure. Crystals of cholesterin are often found, especially in the serous form.

The walls of the cyst may be thick or rigid, or may be thin and soft. The inner surface may be smooth, or, as in the ovarian cyst, may be

covered with papillary formations. It is lined with epithelium derived from the follicles, while there is no epithelial lining in the false cysts of hemorrhagic origin. The walls of the cysts may show calcareous deposits.

In both forms of goiter, colloid and parenchymatous, vascular changes may become so prominent that the arteries and veins are considerably increased in size and number. In such cases an expansive pulsation is present all over the goiter; a thrill is felt on the main trunks of the arteries; a systolic murmur is heard all over the gland. This form is called, clinically, *vascular goiter*. It is usually found in connection with exophthalmic goiter; this vascular goiter, however, may be observed in cases in which no thyrotoxic symptoms whatsoever are present. It is then known as the *non-toxic vascular goiter*.

Both forms of goiter may undergo *amyloid* degeneration, but this is rare.

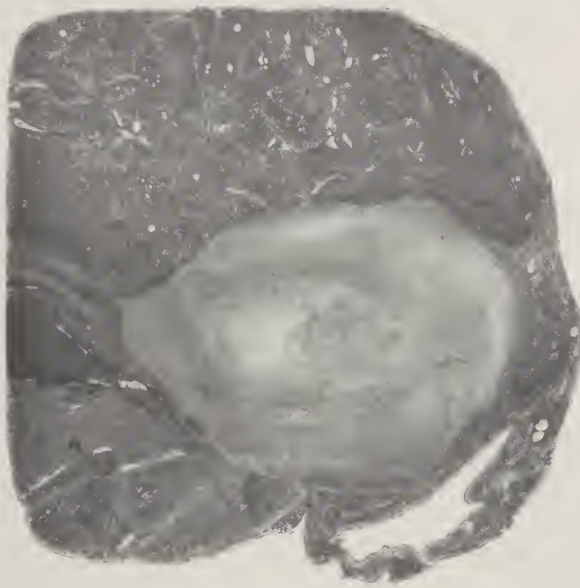


FIG. 12.—Pure fibroma encapsulated in a colloid goiter.  $\times 9$ .

As a result of chronic irritation or inflammation, connective tissue may develop secondarily in a parenchymatous or colloid goiter and thus form a *fibrous goiter* (Fig. 12). Histologically, this is not a new form of goiter, but only the result of a secondary degeneration. The same is true of the *calcareous* deposits which oftentimes take place in goiter, and which may convert a nodular colloid goiter into a hard, calcareous lump. Such conditions should be considered as secondary degenerative changes and should not be regarded as pathological entities by themselves.



**Fetal Adenoma.**—This form of goiter is called fetal adenoma because it is formed from embryonic tissue, because it is of congenital origin,

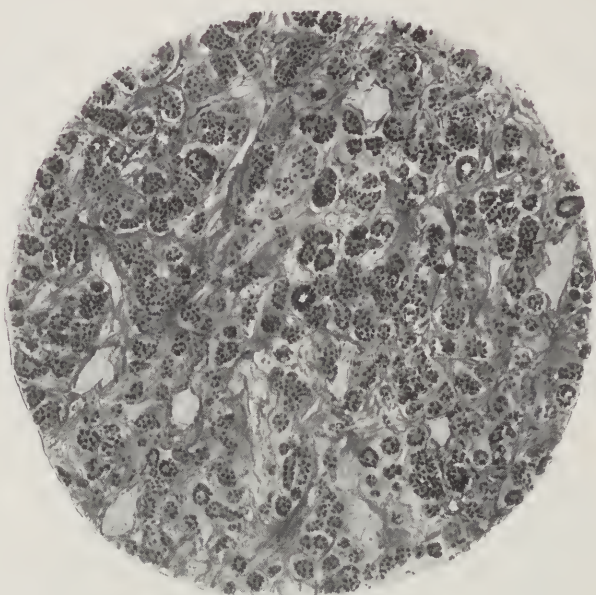


FIG. 13.—Wölfler's fetal adenoma.  $\times 90$ .

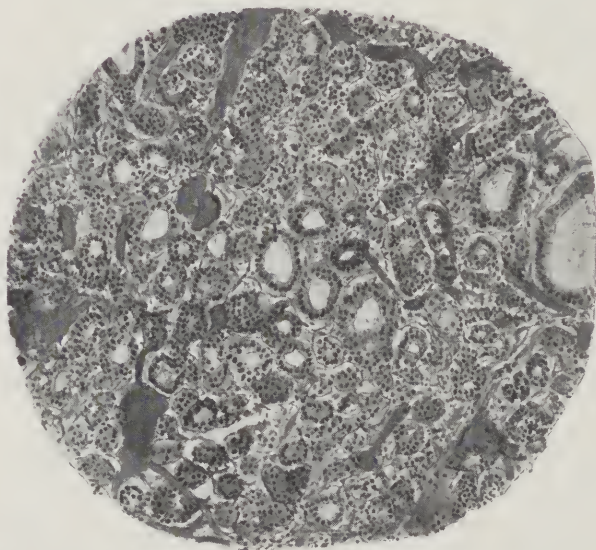


FIG. 14.—Wölfler's fetal adenoma. Alveoli show a tendency toward the colloid type.  
 $\times 100$ .

and because the normal parenchyma of the gland does not take any part in its formation.

The fetal adenoma develops in the early part of life, but is more common at the time of puberty. It seldom exceeds the size of a lemon, but, as a rule, the adenomata are multiple and may reach twenty or more in number. If in a young individual, from ten to twenty years old, several small, round, mobile painless nodules with sharp limits and firm consistency are found, one can be almost sure that they are fetal adenomata. Such goiters generally do not give rise to symptoms except when numerous and large in size; they may then cause pressure symptoms.

Histologically, this goiter is formed from embryonic cells and embryonic follicles. The follicles are small and the cells which line their walls have a fetal character. (Fig. 13, and Plate I, Fig. 2.) They are of medium size and stain intensely. The follicles have a very small diameter and are uniformly of about the same size. The lumen in the early stage does not contain any colloid, but may do so later (Fig. 14); in further development it may be converted into a colloid goiter. The interfollicular connective tissue is very abundant and seems to have a mucoid aspect.

These different forms and varieties of goiters are not found, as a rule, so clearly defined and separated in a goiter as I have described them. Usually, they are mixed together, one form predominating more than the other, and it is this feature which gives to a goiter such a polymorphic, histological aspect.

**Accessory Goiters.**—An accessory goiter is a goiter developed in an accessory thyroid gland. We distinguish two kinds of accessory goiters, the *false* and the *genuine*. If a goiter nodule gradually becomes separated from the main body of the thyroid, so as to be wandering, possibly quite far from the mother-land, while retaining with it a *connective-tissue connection*, this wandering goiter is called *false accessory goiter*; but if the accessory goiter nodule has no connection whatsoever with the thyroid or the goiter then it is called *true accessory goiter*.

Genuine accessory goiter takes its origin in residues left at the time of the formation of the thyroid. We must remember that after the thyroglossus duct has proliferated and formed the thyroid gland, it gradually becomes atrophied and leaves as vestiges a fibrous cord called the thyroglossus tract, which extends from the foramen cecum of the tongue to the pyramidal process of the thyroid, passing between the mylohyoid and the geniohyoid muscles. This duct may leave along its entire course islands of thyroid tissue, at the cost of which later on accessory glands or goiters may develop. Sometimes the thyroglossus tract passes behind or in front, or even through the hyoid bone, and



may extend downward into the anterior mediastinal space as far as the aorta. In that case accessory glands may be left over the entire length of this course and thus will be easily explained the origin of accessory glands and of tumors of the mesobranchial type, developed not only at the base of the tongue, in the hyoid bone, and in the cervical region, but also in the mediastinal space.

But aberrant thyroids and consequently aberrant goiters may be encountered occasionally in the lateral regions of the neck. Thus, Wohl, in 1917, reported a case of a carcinoma of a lateral aberrant thyroid. I recently removed a very large aberrant lateral cystic goiter developed in the upper part of the lateral cervical region, right, and reaching as high as the base of the skull.

The origin of a lateral aberrant thyroid is a matter of speculation, since the ability of the lateral anlage to produce thyroid tissue has been refuted. The most plausible explanation for this occurrence is that during fusion of the ultimobranchial bodies with the median anlage, islands of cells become detached from the median anlage and remain dormant until later in life.

Accessory goiters may be influenced sympathetically by pathological disturbances of the thyroid gland itself; they may undergo compensatory hypertrophy after partial or complete thyroidectomy; finally, they may give rise to the same variety of tumors as the gland itself. Consequently, whenever the presence of an accessory goiter is suspected the thyroid gland should be thoroughly examined, as the treatment will depend greatly upon the conditions found. If the thyroid is functionally intact, excision of the accessory goiter can be done safely; but if symptoms of thyroid insufficiency are present, a partial operation only on the accessory goiter must be performed.

The most important varieties of accessory goiters are the median cysts and lingual goiters; then come the intrathoracic, the intratracheal and the ovarian goiters.

**Thyroglossal Cysts and Fistulæ.**—Thyroglossal cysts and fistulæ, as well as lingual goiter, result from the persistence of the thyroglossal duct, either in part or entire. In order to understand the origin of these thyroglossal cysts and fistulæ, the chapter on Embryology of the Thyroglossal Duct should be read. Only then the reason for these two conditions will become clearly understood. For convenience' sake the *lingual goiter*, which is of thyroglossal origin, will be described separately. Fig. 15 will show the various sites of election where thyroglossal tumors may usually be found.

A persistent thyroglossal tract may give rise to three varieties of lesions. The most common is the thyroglossal cyst; then comes the thyroglossal fistula; finally it may give rise to a solid tumor which may be benign or malignant.

The most common location of the *thyroglossal cyst* is in front of the thyrohyoid membrane, filling up the space between the hyoid bone and the thyroid cartilage. As said before, it is due to the imperfect obliteration of the thyroglossal duct at that point. Thyroglossal cysts may be found above the hyoid bone, in the hyoid bone itself or below it. Although variable in volume, they seldom exceed the size of an egg; they are round or oval in shape, elastic in consistency, sometimes show fluctuation, and are, as a rule, firmly attached to the hyoid bone. They are more or less immobile and painless to pressure. They are never congenital. As a rule, they develop in the first three decades of life and are more frequently observed at the time of puberty.

The walls of the cyst are constituted by layers of connective tissue, more or less thick, and the lining of the cyst is usually composed of cylindrical epithelium, very often ciliated, especially if inflammation has not taken place previously in the cyst. In uninflamed cysts the content is a viscid mucus, somewhat turbid from cell detritus. Cholesterin is often present. If the cyst has undergone inflammation its walls will be much more thickened and the lining of the epithelium more or less destroyed. The contents of the cysts will show all stages of purulency according to the stage of inflammation.

Thyroglossal cysts may remain for many years in a quiescent state, causing practically no symptoms. Only when they become inflamed or when they attain large size do they cause some disturbances.

*Thyroglossal fistulæ* are usually the result of thyroglossal cysts which have ruptured spontaneously or have been opened surgically. The external opening of the fistulæ may be found at any level from the hyoid bone to the suprasternal notch. It may be punctiform or wider, single or multiple. At times the walls of the fistula are so thick as to become easily palpable under the skin, especially in the region of the hyoid bone. Thyroglossal fistulæ pass in front of the incisura of the thyroid cartilage and in front of the thyrohyoid ligament. While passing in front, behind or through the body of the hyoid bone they assume intimate relations with it. The epithelium lining the canal may be epithelial or pavimentous, or both together. It is often of the ciliated type. Secretion is variable and may be reduced to a few drops a day, or, on the other hand, be quite abundant. In that case irritations and eczematous conditions of the skin may follow.

A characteristic of thyroglossal cysts and fistulæ is to be always median, a feature which will distinguish them from tumors and fistulæ of branchial origin, which are always lateral. They may be mistaken sometimes for sebaceous cysts, but a close examination will reveal that the sebaceous cyst, inflamed or not, is in the skin and in front of the muscles, whereas the thyroglossal cyst is below the muscular belt, and unless inflamed does not involve the skin.

The only treatment for such conditions is surgery. When removing thyroglossal cysts, one must be absolutely certain not to leave behind any portion of the wall with its lining, as a recurrence will then take place. When the cyst is found in intimate relation with the hyoid bone it is

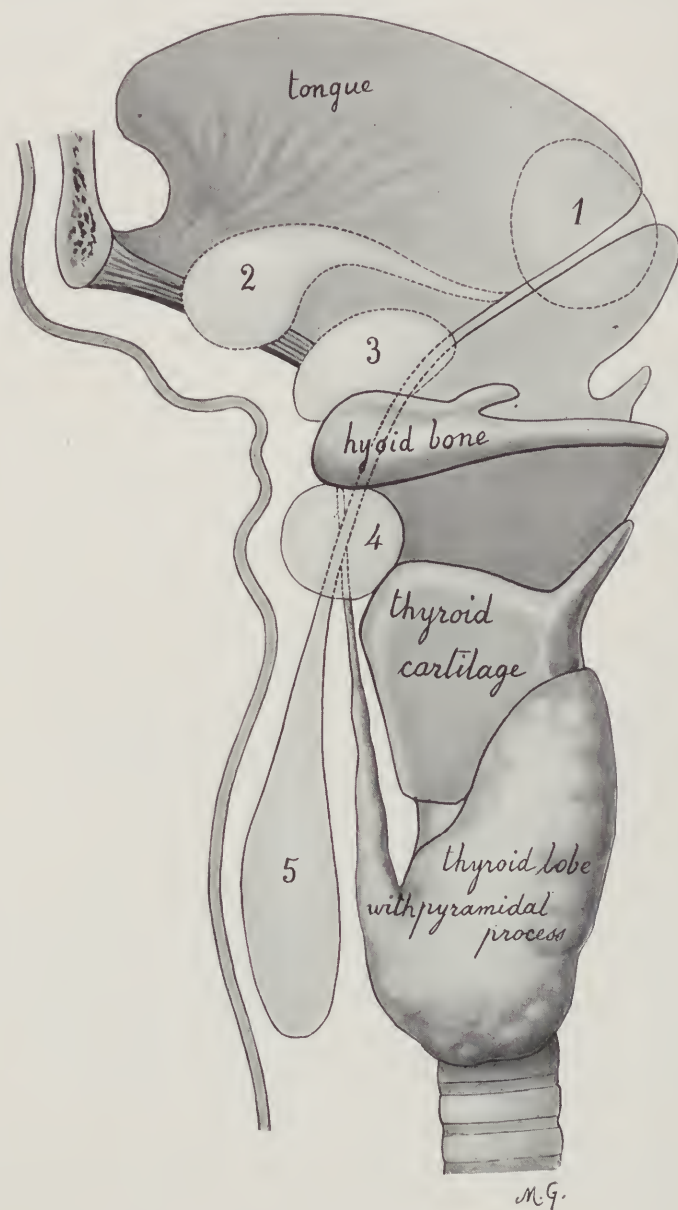


FIG. 15.—Diagram showing the various locations of cystic or solid tumors developed from the thyroglossal duct. 1, intralingual; 2, sublingual; 3, suprahyoid; 4, infrahyoid; 5, prethyroid. (Chemin.)

necessary to curette the bone so as to be sure not to leave any thyroglossal epithelium behind.

Thyroglossal tumors and fistulæ may, in rare cases, undergo malignancy.

**Lingual Goiter.**—Lingual goiter is not frequently found. According to Smyth, 67 cases have been reported in the literature. Out of this number 61 were in females. Although found at all ages of life, they seem to be most frequently reported at the time of puberty. For a long time they may remain unobserved, but when they begin to grow the symptoms rapidly become marked.

The tumor is always found at the root of the tongue in the region of the foramen cecum, and is usually median. The size varies between the size of a cherry and that of an egg. Its consistency is variable; it may be hard, soft or cystic, according to the pathological changes which have taken place in it. The surface is usually smooth, but if cysts or colloid nodules are present, it is irregular. Although embedded in the muscular fibers of the tongue, it may have a slight mobility *per se*, and has always, except when inflamed or degenerated, very sharp limits. Under the chin the limits of the tumor are more or less diffuse on account of the thickness of the tissues interposed.

Lingual goiters are exceedingly vascular. Large, numerous bloodvessels penetrate the goiter from the neighboring tissues. The mucous membrane of the tongue over the tumor is congested and filled with dilated bloodvessels, consequently a slight traumatism may cause quite an important hemorrhage; as a result the operation will be a bloody one. Furthermore, on account of the great vascularity it has a much darker color than the surrounding mucous membrane. Histologically, these tumors are the same as simple goiter.

The symptomatology of such tumors has very few characteristics of its own. Patients complain of a sensation of fulness and tension in the upper part of the neck as if a foreign body were localized in the pharynx and could not be swallowed despite continued efforts at deglutition. If the tumor is superficially localized, the epiglottis being constantly irritated, coughing spells may ensue. Deglutition and respiration are, as a rule, interfered with only when the goiter has reached larger dimensions. There is often a certain difficulty of speech: the patient articulates as if the tongue were infiltrated and swollen. At the same time the flow of saliva may be increased; expectorations of blood due to ulceration of the lingual mucous membrane may occur.

Diagnosis is not always easy. In discussing the differential diagnosis of lingual tumors the possibility of a lingual goiter should always be borne in mind. The mere inspection of the buccal cavity with a frontal mirror is not sufficient, as in many of the reported cases the



tumor could not be seen by direct inspection. But indirect examination with the laryngoscopic mirror will show in the region of the foramen cecum a tumor bulging more or less and covered with a congested and vascular mucous membrane. Bimanual palpation with one finger in the mouth and one beneath the jaw will readily discover the tumor; as palpation is painless, its limits will be easily outlined. Lymphatic glands of the cervical region are not involved.

In a syphilitic gumma of the tongue the limits are more diffuse and softening of its central portion may be present. In malignant tumors the limits will be infiltrated and diffuse. The age of the patient and the course of the disease may be of some help in differentiating the diagnosis. Dermoids and cystic tumors of branchial and salivary origin sometimes found at the basis of the tongue may not be differentiated, clinically, from a lingual goiter, as their consistency and other anatomical features may recall those of a lingual goiter to such a degree that their true nature is recognized only at the time of the operation. Angiomata are more spongy, more irregular in outline, of purple color, and show usually venous extension to one of the lateral sides of the pharynx.

Surgery is the only rational treatment for such conditions. The operation can be made from within or without the mouth. The choice of the route will be dictated by the case itself. If the buccal route is chosen, and if general anesthesia is not used, the tongue and pharynx are carefully novocainized, and a rapid enucleation is made while the tongue is held in extreme tension. The free hemorrhage is controlled by deep sutures. If the cervical route is chosen a transverse incision is made in the region of the hyoid bone and the goiter is dissected out. It will rarely be necessary to divide the lower jaw. While bloody, these operations for lingual goiter are quite successful. Fatalities are rare.

Before undertaking the complete removal of a lingual goiter one should ascertain that a thyroid gland is present. If it is not, symptoms of thyroid insufficiency will follow. Indeed, quite a number of cases have been reported where the only source of thyroid secretion proved to be the lingual goiter alone. Under such conditions it is easy to understand that the radical removal of the lingual goiter will lead fatally to hypothyroidism. To illustrate:

In 1897, Seldowith removed a lingual goiter in a girl, aged fourteen years. On palpation no thyroid gland could be felt. Some time later the girl died with symptoms of cachexia strumipriva.

In 1898, Aschoff reported the case of a myxedematous infant, aged six months, with a total absence of thyroid and the presence at the base of the tongue of a cystic goiter the size of a pea.

The same year, Chamisso removed a lingual goiter the size of a walnut from a cretin, aged thirty-seven years. While performing



tracheotomy as a preliminary step to the operation, search for the presence of a thyroid gland was fruitless. Five months later the patient showed all the signs of cachexia strumipriva.

In 1906, Dieterle reported the case of a female child, aged three months, markedly myxedematous and with the thyroid totally absent, but possessing a small cystic thyroid tumor in the region of the foramen cecum.

In 1907, Ungermann reported 25 cases of a similar nature.

In 1908, Erdheim reported 2 cases of hypothyroidism, 1 in a child, aged three months, and the other in a child, aged eight months. In both cases the thyroid was absent as shown by postmortem, but in both cases a small cystic thyroid tumor was present at the base of the tongue.

Ungermann reported the case of a man, aged thirty years, who died following the excision of a tuberculous ulcer of the lip and who on postmortem showed at the foramen cecum of the tongue the presence of a small colloid nodule the size of a chestnut. No thyroid gland was found except that on the right side there were two small nodules the size of a pea, which proved to be on microscopic examination of a thyroid nature. No signs of thyroid insufficiency were present during the life of the patient.

Many other cases could be cited to show that in such instances the lingual goiter was the only source of thyroid secretion in these given cases. From the clinical standpoint it is consequently of primary importance to recognize the presence of a thyroid gland before removing totally the lingual goiter. When the isthmus is absent so that the tracheal rings from the cricoid cartilage downward can be felt plainly, and when no lateral lobes can be outlined, it might be safer for the future clinical welfare of the patient to leave behind a little bit of thyroid tissue when removing the lingual goiter.

**Intrathoracic Accessory Goiter.**—Accessory thyroid glands are not infrequently found in the thorax. Wölfler called attention to this, and Wagner found quite frequently small accessory goiters in the thoracic cavity of dogs. I remember finding at an autopsy of a patient a tumor the size of a small egg situated at the bifurcation of the trachea. Histologically, this tumor was a simple colloid goiter.

These tumors have been found in close relation with the aorta, and therefore have been called *aortic goiter*.

While assistant to Professor Kocher I remember seeing an aberrant intrathoracic goiter which, during coughing spells, became cervical and disappeared again into the chest.

The majority, however, of these tumors are autopsy findings. Few may grow so large that marked symptoms of dyspnea and impairment

of circulation follow. The symptomatology of such tumors does not differ from the symptomatology of intrathoracic goiter, which will be discussed in a later chapter.

**Ovarian Goiter.**—Ovarian tumors showing both grossly and histologically the typical structure of a struma colloidæ have been reported by authors more than once. A great many of such tumors are teratomata in which the thyroid tissue has taken the upper hand, but in others no teratoid formations can be found, so that the tumor seems to be composed purely of thyroid alveoli with their typical normal structure.

Possibly such tumors are due to metastatic colloid goiters. We know that a simple colloid goiter is liable to make metastases in bones and other organs. Why not, then, in the opinion of some authors, admit that such metastases could take place in the ovary? Thus the question is proposed, but I would not dare to answer it. I should rather be inclined to consider the above theory as improbable.

Similar tumors have been found in the testicles. One should not forget there is a series of tumors which might be mistaken for an ovarian goiter, and which are, indeed, tumors of an entirely different nature, such as adenoma, cystadenoma, adenocarcinoma, endotheliomata, etc.; in these, too, the colloid formation may be very abundant and the histological picture may resemble that of goiter.

Pick was the first to contend that these ovarian goiters are all teratomata, whether they contain or do not contain embryonic rests of other organs; the thyroid elements possessing more vitality outgrow the other embryonic tissues and finally destroy them. This process results finally in the production of a colloid tumor. In support of his contention, Pick cites Saxer's case, in which a single well-formed tooth was found in an otherwise healthy ovary. In Pick's judgment this can be explained only on the theory that a teratomata had started to develop, that the tooth above was able to grow, and that the remainder of the embryonic tissues was absorbed.

Pick's views on the etiology of ovarian goiters are, so to speak, universally accepted. Walthard examined three ovarian goiters which were apparently composed of thyroid tissue only. Yet after making "complete serial sections" of all of these three tumors he found in one case cartilage, in the other squamous epithelium, and in the third sebaceous and sweat glands. In every case the findings were purely *microscopical*; it would have been utterly impossible to detect them macroscopically. These facts of Walthard's very strongly support the teratoma theory.

The iodine content of such tumors might be of diagnostic value, since we know that in goiter, iodine more or less is always present. To be pathognomonic it should be demonstrated that iodine does not exist

in any others except in those of thyroid origin. I think that this fact has not been thoroughly established. At any rate the amount of iodine found in these thyroid-like tumors is so infinitesimal (0.000225 gm. iodine in 16 gm. of ash, by Robert Meyer) that its presence is of comparatively little significance. A. P. Jones has shown that the presence or absence of iodine in colloid material can be determined by the behavior of the colloid with the Mallory aniline-blue-orange connective-tissue stain. G. W. Outerbridge, after applying the same staining method to ovarian goiters, found that these tumors contain without doubt a certain amount of iodine.

Such tumors may reach a very large size and are very often accompanied by ascites; they are coarsely lobulated and may be partly cystic and partly solid. The only case which it has been my good fortune to see, reminded me at once on its cut surface of a colloid goiter; the histological examination confirmed my presumptions. Clinically, most of these ovarian goiters are benign; some of them, however, may undergo malignancy. Concomitant *ascites* must be regarded as a suspicious symptom. Yet it is no certain proof of malignancy, since we know that ascites sometimes accompanies benign ovarian tumors or non-malignant pediculated fibroids of the uterus.

From all that we know of the physiology of the thyroid gland, if these ovarian goiters are truly of thyroid parenchyma, then there can be no doubt that these tumors are endowed with an *internal secretion*.

### MALIGNANT GOITERS.

We distinguish tumors developed from the epithelium and tumors developed from the connective tissue of the thyroid gland. To the first class belong the *epithelial neoplasms* and to the second the *connective-tissue tumors* or *sarcomata*.

One of the chief characteristics of a malignant goiter is its tendency to metastases.

*Metastases* of malignant goiter, whether of epithelial or connective-tissue origin, may take place through the lymphatics or through the bloodvessels. The general formula applied to malignant tumors when speaking about their mode of dissemination: "Hematogenous route for sarcomata, lymphatic route for cancerous tumors," does not hold good any longer here.

Metastases of epithelial malignant goiters occur more frequently in bones than metastases of sarcomata. In both varieties, metastases in the lungs are very frequent.

In going over statistics of cancer in general it has been found that cancer of the thyroid occupies the most prominent place so far as metas-

tases in bones are concerned; then comes cancer of the prostate. Hassner, for instance, finds that in 140 cases of cancer of the thyroid there were 34 cases of metastases in bones, making 24.3 per cent; in 1358 cases of cancer of the breast, only 106 metastases in bones, making 7.8 per cent; in 203 cases of cancer of the uterus, 7 cases of metastases in bones, making 3.4 per cent; in 247 cases of cancer of the kidney, 9 cases of metastases in bones, making 3.7 per cent; while in 903 cases of cancer of the stomach not a single metastasis in the skeleton was found.

Metastases of malignant thyroid tumors show a marked predilection first of all for the skull, then follow the pelvis, sternum, femur, clavicle, lower jaw and the shoulder-blade. Metastases in bones, as a rule, are not multiple.

Recklinghausen, trying to explain the reason why bony metastases of malignant tumors of the thyroid were so frequent, thought that in bones, on account of the sudden widening of the venous spaces, the blood stream takes a slower course, thus offering the possibility and time to cancerous cells to become permanently settled and then to grow. That may be so, but this theory does not explain why cancers of the thyroid are the ones which develop metastases in bones much more frequently than cancers of the other organs of the body.

One peculiarity of these malignant metastases is their ability to revert to the normal type of thyroid tissue; in other words, if a microscopic examination of such metastases is made the malignant character of the tumor may have disappeared entirely, or have diminished to such an extent that the microscopic picture is mostly one of normal glandular structure. Cramer explains this by saying that in metastases few cells, partly malignant and partly normal, are carried away into the blood stream, and that cancerous cells, being more resistant than the normal ones, grow first, and only then under their protectorate normal cells proliferate, outgrowing later on the cancerous ones. "Se non é vero é ben trovato."

Meyer-Hürlimann and Ad. Oswald had the opportunity to observe a remarkable case of cancer of the thyroid. After  $x$ -ray treatment the tumor softened and began to secrete an enormous amount of a serous, brownish-yellow fluid which chemically and physiologically showed the same properties as normal thyroid secretion. This shows that malignant degeneration of the thyroid does not deprive the latter organ of its normal function.

The faculty of these cells not only to shape themselves into normal alveoli, but also to secrete colloid, raises one of the most interesting problems of *ontology* and *teleology*. How is it that malignant cells which cannot be differentiated from normal ones will be carried away by the



blood stream, and will not only grow upon a strange land but will also not be deprived of their physiological action, which is the colloid secretion? A similar feature does not occur in cancerous metastases of other organs. Metastases of the breast do not secrete milk, nor does a metastasis of the liver secrete bile, nor does a metastasis of the cancerous kidney secrete urine. Who can give the answer?

That such metastases are capable of normal physiological function is a very well-known fact. Classical is the case of von Eiselsberg, who performed a complete thyroidectomy for a malignant tumor. Nothing worth notice followed the operation, but later on, when in a subsequent operation a metastasis was removed, marked symptoms of myxedema soon developed.

Malignant tumors of the thyroid seem to have a peculiar tendency to penetrate the walls of the veins even in the early stage of their growth, and it is not uncommon indeed, at operations of cases which clinically seem to be most favorable, to find the thyroid imæ veins thrombosed and already invaded by the tumor.

It is to the Bernese pathologists, Langhans and his pupils, that we are really indebted for what we know of the malignant epithelial tumors of the thyroid. Their classification is based upon the fact that embryological remnants of various organs may remain included in the thyroid gland and give rise to tumors at one time or another.

*Epithelial tumors.*

1. Malignant adenoma or proliferating goiter.
2. Carcinoma.
3. Metastatic colloid goiter.
4. Parastruma.
5. Postbranchial goiter.
6. Papilloma.
7. Cancroid.

**Malignant Adenoma or Proliferating Goiter.**—This has been called *adenocarcinoma* by von Eiselsberg and *malignant adenoma* by Kocher. The denomination, proliferating goiter, applied to that form of tumor, might be confused with the hyperplastic goiter which is not malignant. Therefore I prefer, especially from a clinical point of view, to adopt the denomination of Kocher: malignant adenoma.

Macroscopically, it is usually represented by a single nodule or growth of a diameter ranging from 10 to 15 cm.; it is seldom larger. I have, however, operated on a malignant adenoma involving both lobes and isthmus, very vascular, each lobe measuring about 20 x 15 x 10 cm. Occasionally, the tumor may be formed by more than one nodule. Its surface is lobulated and the capsule is more or less thick. Inwardly, septa divide the parenchyma into lobi and lobuli, while in or near the center of the



nodule there is a more or less constantly necrotic area giving the tissue a scar-like appearance. The cut surface is like marrow, of a grayish-white color, and more or less cloudy juice can be expressed. Microscopically, the tumor is formed by regular, polyhedric lobuli with round corners, resembling very much normal enlarged follicles (Fig. 16). Between them are found capillaries composed merely of an endothelial wall, with no adventitia, and with no muscular and elastic fibers (Fig. 16). Affecting a lacunary form (Plate II, Fig. 1) instead of a round shape, as ordinary capillaries do, they lie in direct contact with the

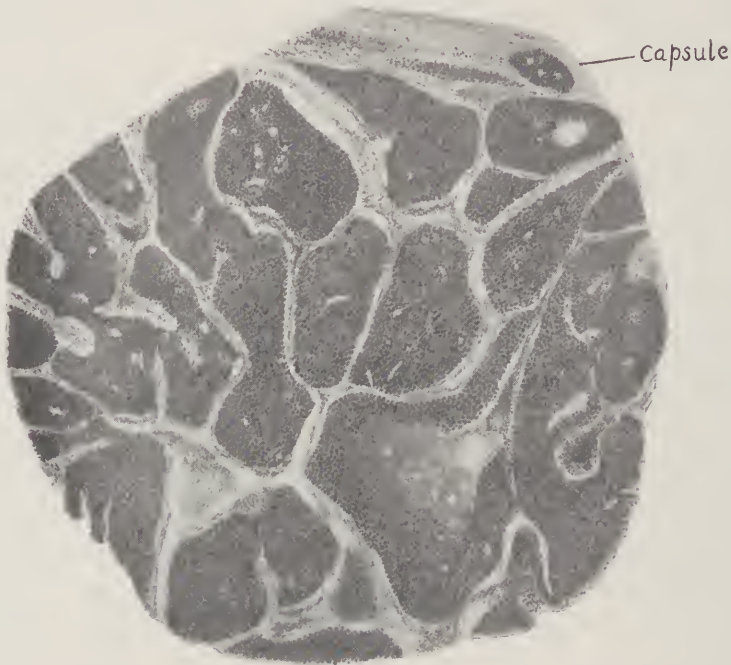


FIG. 16.—Malignant adenoma. Periphery of the tumor. Above, capsule infiltrated with malignant cells; below, large polyhedric fields of cells, forming solid cellular masses separated by trabecules of connective tissue.  $\times 50$ .

tumor cells. (Plate II, Fig. 2.) In some instances they surround the lobuli entirely, forming then what Minot called "sinusoids."

The above microscopic picture found even in a very small particle of a tumor or of a metastasis is pathognomonic for the malignant adenoma or proliferating goiter.

Cells have a polyhedric form, and at the periphery of the nodule they are better nourished and younger than in the center. Their protoplasm is finely granular and their nuclei are round or oval, measuring from 6 to 10  $\mu$ . Most of them contain one or more nucleoli.

## PLATE II

FIG. 1



Malignant Adenoma.

Large vascular lacunary formations cut transversely and surrounded by cellular masses. This picture is typical too for the malignant adenoma.  $\times 50$ .

FIG. 1



Malignant Adenoma.

Capillary vessels are formed by an endothelial wall without adventitia. Note their lacunary forms. Note in *a* the close relation between the tumor cells and the endothelium.  $\times 280$ .



In places small foci of undifferentiated cells gradually shape themselves into the form of a circle in which colloid appears, thus forming a new vesicle. These neoformed vesicles, when considerable in number and seen at a low power, give to the field a peculiar, screen-like appearance, characteristic, too, of the proliferating goiter or malignant adenoma. Since, later, connective tissue appears between these vesicles, this neoformed tissue has a great similitude with a normal thyroid gland. The scar-like tissue found in the center of the tumor is formed of newly organized connective tissue; it is a product of necrosis.

Metastases take place preferably in the cranium and lungs through the bloodvessels; lymphatic glands are not involved.

Histologically, the malignant adenoma differs entirely from the ordinary cancer. In malignant adenoma we have not, as in cancer, irregular epithelial masses surrounded by a more or less developed and irregularly shaped frame of connective tissue. As Langhans says, the malignant adenoma with its peculiar formation, with its neoformed vesicles lined with one layer of epithelium and containing colloid, with the peculiar shape of its bloodvessels, with the irregularity of their disposition, of the construction of their walls and their intimate relation to the epithelium, recalls rather a normal organ in the course of development than a cancer. Hence the name *proliferating goiter* given by Langhans.

Does the malignant adenoma develop from goitrous elements themselves or does it develop from embryonic rests of undifferentiated normal thyroid tissue? Langhans thinks that the second alternative is likely to be true.

**Carcinoma.**—Cancer of the thyroid is a hard, nodular tumor, as a rule, firmly adherent to the neighboring tissues. The cut surface is a grayish white. Typical cancer juice can be expressed. This carcinoma has a tendency to undergo softening of its constituent parts.

Histologically, this cancer shows the usual microscopic picture which is found in cancer of the breast, stomach, etc., namely, the same interrelations between connective tissue and epithelium which enable us to diagnose cancer. Here, too, as in cancer of other epithelial organs, we have cellular masses irregularly disposed, surrounded by an irregularly developed stroma. The cancer cells, in opposition to the normal cells of the thyroid, have a poorly developed protoplasm; they are small; their nuclei are larger than those of a normal gland and measure from 10 to 16  $\mu$ .

In cancer of the thyroid, metastases may take place in the sternum, ribs, pleura, kidneys and in the suprarenal bodies. The cancer does not penetrate the bloodvessels as the malignant adenoma does; metastases occur through the lymphatic route; hence involvement of the cervical and possibly of the mediastinal lymph nodes.

It is not always easy to decide microscopically if a metastasis comes from a cancer of the thyroid or not. If in the metastasis vesicles containing colloid are found the diagnosis is easy. If not, the size of the cells and their nuclei, their number and their close relation of one to another will arouse a strong suspicion in favor of their thyroidal origin.

**Metastatic Colloid Goiter.**—Metastatic colloid goiter, histologically, does not differ in any way from a simple colloid goiter. There is nothing in its histological picture to arouse the suspicion of malignancy. In the metastatic as well as in the primary tumor we find follicles of different forms, round, oval or elongated. The epithelium of such vesicles may be cuboidal or cylindrical. The colloid material is as abundant and has the same staining power as the colloid of a simple goiter. It may be strongly colored by eosin or its coloring power may be diminished or totally absent. Lymphatics and bloodvessels are normal and do not contain metastatic cells. The capsule of the nodule is absolutely intact. The only feature is its metastasizing power.

Metastases in the great majority of cases take place through the vascular route; they may, however, occur through the lymphatics. In that case metastases are found in the cervical, mediastinal and bronchial lymphatic glands. But the seat of predilection of such metastases is in the spinal column, sternum, ribs and long bones.

Tumors of bones due to metastatic colloid goiter form an interesting pathological chapter. Clinically, their true origin is not recognized. They are considered as sarcomata, and it is only at the microscopic examination that the error is discovered. Cohnheim, who was the first to report a case of metastatic colloid goiter in bones, considers these tumors as benign; but Recklinghausen and Wölfler do not share the same view and consider them as malignant, claiming that a tumor which is capable of giving rise to metastases is not entitled to the denomination of benign tumor. In Wölfler's judgment this metastatic tendency indicates an increased proliferative energy, which is one of the chief characteristics of malignant tumors. Despite the authority of such men, Bontsch, Honsell, Oderfeld, von Steinhaus, Karl Schmidt, Patel, etc., have taken exception to such conclusions and consider a metastatic colloid goiter as a benign tumor. On the other hand, Kaufmann, Borst and Hanse-mann are unanimous in considering such tumors as malignant. In their judgment the denomination of "benign" applied to a tumor which is capable of metastasis is certainly in contradiction to what we know of benignancy. Langhans, too, considers this tumor as a malignant one.

It cannot be denied there are cases in which the metastatic organ was found to be, histologically, a simple goiter, which after surgical removal never gave any recurrence. The only sign of malignancy was its metastatic feature. On the other hand, metastases of benign tumors,



as fibroma, myoma, adenoma, have been reported by good authorities. We know that normal organs, as placenta, liver and suprarenal bodies, whose cells are in intimate relation with bloodvessels, may cause metastases without having shown any sign of malignancy. Why should not this be possibly the case for the thyroid gland? Cohnheim reported a case of simple goiter in which he was able to find, microscopically, epithelial cords penetrating the walls of a vein and floating freely into the lumen. In such conditions metastasis is easily understood. At any rate, for some reason or other, a few normal cells are carried away by the blood stream into other organs. Under ordinary circumstances these cells would decay, but for some unknown reason they find a favorable "terrain" on which they grow and finally develop to the size of a tumor. This feature is no longer to be wondered at since the illuminating experiments of Carrel, who has been able to grow in cultures normal cells of different organs.

If we accept Ehrhardt's definition of a malignant goiter, "An intra- or extracapsular tumor whose elements invade the capsule, encroach upon the neighboring tissues and cause metastases," we will see that in the metastatic colloid goiter the encroaching upon the neighboring tissues and the invasion of the capsule by the glandular elements are absent. The metastatic feature is the only remaining sign of malignancy.

What strikes me in the history of a real malignant goiter is that there usually was at first a simple goiter of more or less long standing, that it suddenly began to grow rapidly, and only later on gave rise to metastases in the organs. This is not the case of the metastatic colloid goiter; there is here no such history as that of the rapid development of a tumor. Furthermore the metastatic colloid goiter has little or no tendency to produce cachexia. Regensburger, in going over the statistics of 58 cases, found that the time which elapsed between the beginning of the metastases and the death of the patient was from one to seventeen years. In all cases death was not due to the goiter but to an intercurrent disease. Therefore I am rather inclined to regard metastatic colloid goiters as being in most cases, *benign tumors*.

**Parastruma or Glycogen-containing Goiter.**—Dr. T. H. Kocher, Jr., was the first to describe this form of goiter. It has a nodular appearance, grows rapidly and soon becomes adherent to the neighboring tissues; it is very hard in consistency and rapidly causes pressure symptoms. The cut surface is gray or grayish white and shows a typical, irregular, alveolar structure.

Its cells are large and clear and measure in diameter from 20 to 30  $\mu$ . They are polyhedric, sharply outlined with a colorless colloid body, and have no granular protoplasm staining with eosin. Such cells contain

glycogen in variable quantity, detected by specific stainings. Nuclei are round and vesicular.

Smaller granulated cells, staining with eosin, not so sharply outlined as those previously described and not containing glycogen, are usually distributed all over the tumor and mixed with cells containing glycogen.

The alveoli are separated by septa formed by capillaries which have the same lacunar aspect as the ones spoken about in the proliferating goiter. In between the alveoli glandular canals lined with cylindrical cells disposed in two or more layers are found. Their nuclei, instead of being at the base, lie at the tip end of the cell near the alveolar lumen. They are of embryonic origin and correspond to the vesicles and canals which Kürsteiner found extending from the lower portion of the parathyroid bodies to the upper part of the thymus gland. They have about the same dimensions as the tubuli contorti of the kidney, and possess a high, clear, cylindrical epithelium with a *nucleus lying at the upper tip end of the cell*. Such canals may be found even in the thymus itself; they disappear at birth.

On the other hand, Getzowa discovered in normal thyroids residues of aberrant parathyroids containing glycogen and glandular cells, resembling entirely those above described. We know that the human parathyroids usually contain glycogen; that they contain sometimes glandular canals lined with a high, clear, cylindrical epithelium whose nuclei lie at the upper pole of the cell. Therefore it seems safe to conclude that a tumor containing glycogen and whose cylindrical cells have a nucleus at the tip end of the cell instead of at the base, is derived from the parathyroid bodies; hence the name *parastruma*.

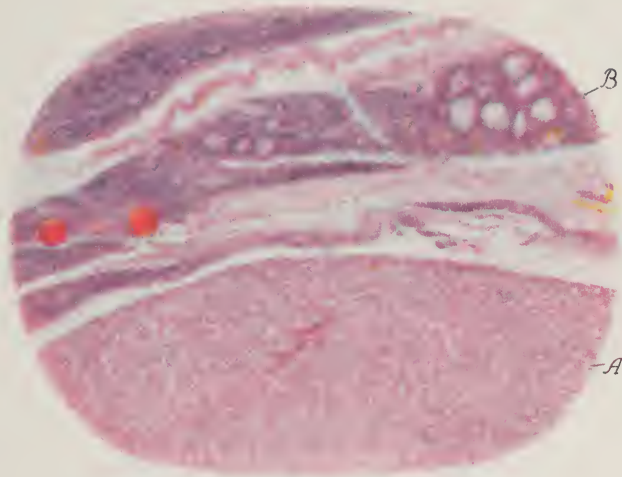
Parastruma gives metastases in the cervical, mediastinal, bronchial glands, lungs and bones. Metastases may or may not contain glycogen but possess the same characteristic cells; they contain, too, a great quantity of mucine not found in the parathyroid bodies.

**Postbranchial Goiter.**—Macroscopically, this tumor is composed of large nodules of more or less irregular surface, sharply outlined from the rest of the gland. The cut surface is alveolar, shows fine granulations and is of a grayish-brown or grayish-red color. This tumor grows very rapidly.

The alveoli are very small and seldom have a diameter of more than 100  $\mu$ . The cells measure from 15 to 30  $\mu$ , and show a large homogeneous, refringent protoplasm. They are polyhedric; their nuclei have about the same size as the nuclei of normal thyroid glands; they are round, vesicular, and contain small corpuscles of chromatin; a small eccentric nucleoleus is almost always present. Such cells stain intensely with acids and do not contain fat or glycogen.

# PLATE III

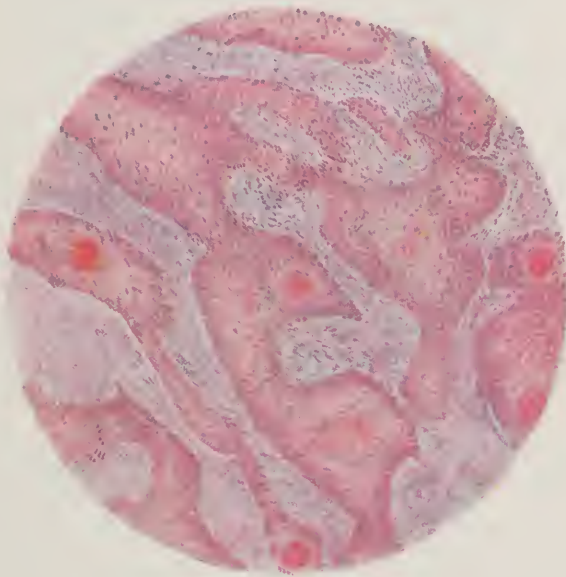
FIG. 1



Struma Postbranchialis.

Nodule *A* sharply outlined from the rest of the gland. Note how staining *A* differs from staining of thyroid epithelium *B*. *A* forms a cellular mass suggesting alveoli formations in places.  $\times 62$ .

FIG. 2



Canceroid.

Typical cancerous pearls.  $\times 70$ .



They resemble greatly the cells of the liver or of the suprarenal bodies. Their vesicular arrangement and their colloid content show their true origin and prevent mistaking them for the liver's or the chromaffin system's epithelium.

Metastases are found in the lungs, liver, in the lymphatic glands of the neck and of the mediastinal space, and occur through the lymphatic vessels.

Getzowa has found in normal thyroid glands groups of cells having exactly the same histological appearance as the cells described. They are polyhedric, with an abundant granulated protoplasm, staining intensely with eosin. (Plate III, Fig. 1.) The cells are sharply outlined

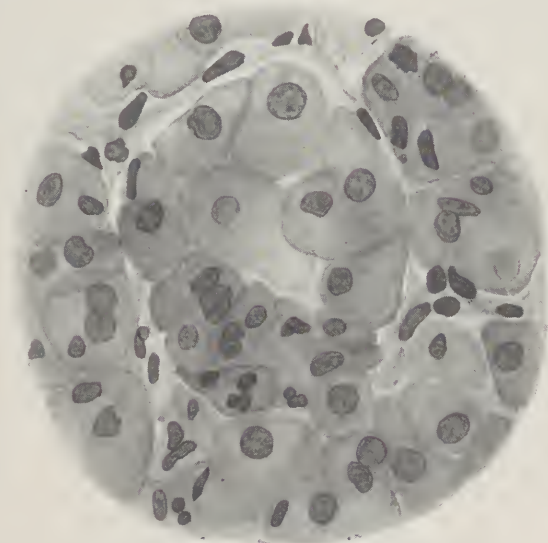


FIG. 17.—Struma postbranchialis. Large cells resembling liver cells. Note large homogeneous body of protoplasm with round, vesicular nuclei containing small corpuscles of chromatin and in places an eccentric nucleole.  $\times 700$ .

and resemble the liver cells (Fig. 17). They form solid cellular groups, and in places beautifully formed vesiculi containing colloid. They are embryonic residues of the *postbranchial bodies*, hence the name *postbranchial goiter*.

**Papilloma.**—Papillomata are usually small in size, and may have a diffuse or nodular form. The nodules are small, smooth in surface, with a firm, fleshy consistency. The cut surface is finely granulated, grayish red, and may show a lobular structure. The tumors may be solid or cystic. In the cystic form the most striking and arborescent papillary formations may be seen sprouting from the walls of the tumor into the interior of the cyst (Fig. 18).



A papilloma begins its development in a small follicle lined with one layer of epithelium. At first, there is proliferation of the epithelium in one point; this will constitute the first step toward the formation of a papilla. It gradually grows larger, and in a later stage subdivides into smaller branches which subdivide themselves again, finally giving rise to the most complicated arborization (Fig. 19). In places the branches of the arborizations may fuse together and form vesicles in which colloid may be found (Fig. 20). Capillary vessels penetrate only later in the axis of the papilla and of the arborizations.



FIG. 18.—Papillomata partly cystic and partly solid. In the solid portion the papilla fill up the whole space. In the cystic portion exquisite arborizations are seen.

The cells are generally large and provided with an abundant protoplasm, granular, not refringent, and staining readily with eosin. Whether cuboidal or cylindrical, these cells may be sometimes very high and may reach  $40\ \mu$ . The nuclei are round or oval, lying at the base of the cell or *at its tip*. They contain a nucleolus staining with eosin.

Papillomata metastasize especially in the lymphatic glands, and have a great tendency to encroach upon the neighboring tissues. Metastases have the same histological picture as the primary tumor.

In such tumors lymphoid masses may be found, many of them possessing a distinct germinal center. The fact that cells with nuclei at their upper end are found, shows that these tumors very likely take their origin in the Kürsteiner canals, described in relation with postbranchial goiter.

**Cancroid.**—This tumor never reaches enormous dimensions. It has an irregular surface, is very hard in consistency, and may occur in normal thyroid gland as well as in preëxisting goiter. The cut surface is whitish, a marrow-like color, and is finely granular; the granulations are formed by cancerous nests sticking out, and readily expressed.

Histologically, this tumor gives the same microscopic picture as the cancroid developed in the skin, mouth, pharynx, esophagus and other organs containing a cuboidal epithelium. It is formed by broad, solid cords of irregular size and form (Fig. 21) embedded in a more or less

loose connective tissue and formed of polyhedric cells provided with an abundant protoplasm. This protoplasm is finely granular and does not

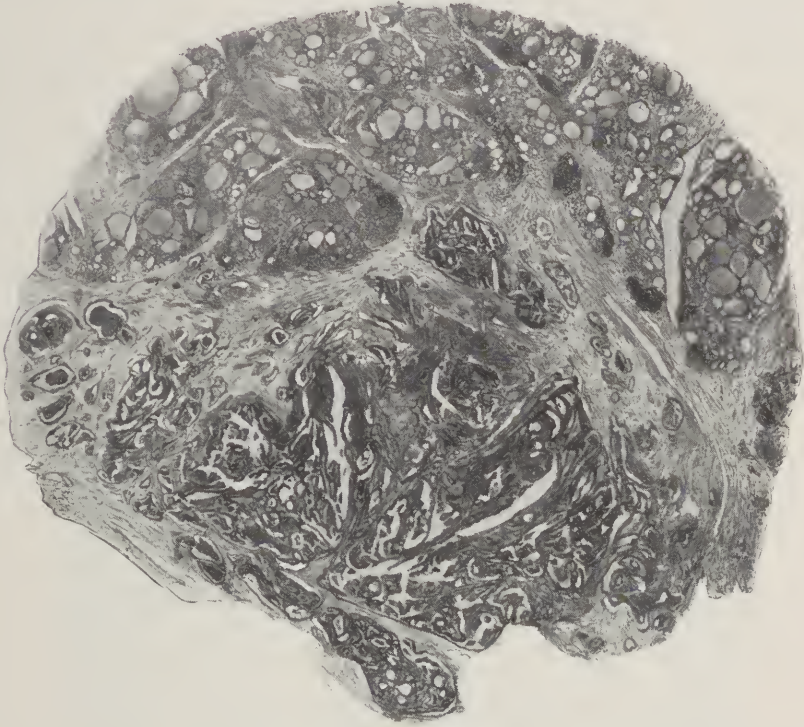


FIG. 19.—Papillomata. This low power shows plainly the arborescent formations.  $\times 17$ .

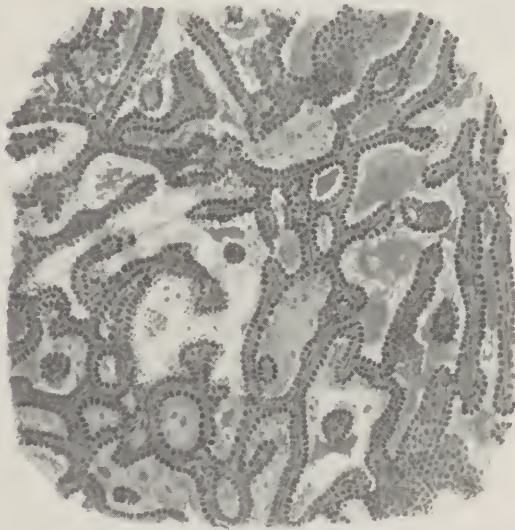


FIG. 20.—Papillomata. Low cylindrical epithelium and alveolar formations containing colloid.  $\times 125$ .

take eosin easily. It contains in its center a very large vesicular nucleus which contains a few small nuclei of chromatin. (Plate III, Fig. 2.) *Cancer pearls* are numerous; the blood supply is not diminished, and the stroma is generally highly developed.

Owing to the fact that cancrioids of the thyroid have always a close connection with the pharynx or larynx, Langhans thinks that these tumors have their starting-point in the epithelium of the pharynx, larynx or in remnants of the thyroglossal duct. The fact that these tumors always develop and perforate at the same place, namely, near and behind



FIG. 21.—Cancroid. Broad, solid, cellular cords of irregular size and form embedded in more or less loose connective tissue.  $\times 44$ .

the first tracheal ring, seems to support this theory. On account of their communication with the larynx or pharynx these tumors are oftentimes the seat of inflammation and have a tendency to necrosis. Being given their anatomical relations they involve the sympathetic and inferior laryngeal nerves early. Cancroids of the thyroid are rare.

**Tumors of Connective-tissue Origin.**—Sarcoma of the thyroid gland occurs sometimes in early life, but in the great majority of cases it is to be found between fifty and sixty years. Molf thinks that he found a suitable explanation for this in the fact that in advanced age, epithelial



elements undergo atrophy, thus allowing the connective tissue to grow with energy.

Sarcoma develops with preference in nodular goiter, where the connective tissue may be found more or less abnormally developed and undergoing degenerative and metaplastic changes. It may reach larger dimensions, being formed by a mass of conglomerated nodules, more or less large in size.

Sarcoma grows extremely rapidly. In the early stage it is mobile and sharply limited, but later it becomes adherent to the neighboring tissues, muscles, trachea, esophagus, etc. Hence the diffuse limits, loss of mobility, difficulty in swallowing, irradiating pain in the ear, in the arm, etc. The common carotid is displaced backward; exceptionally, it may be completely surrounded by the tumor. Sarcoma is soft in consistency, friable, exudes little juice or none on its cut surface, which is grayish white in color. Its blood supply is generality increased. It has a great tendency to undergo necrosis, fatty degeneration or calcification.

The varieties of sarcomata found in the thyroid gland are:

1. Fibrosarcoma.
2. Polymorphous-cell sarcoma.
3. Round-cell sarcoma.
4. Myxosarcoma.
5. Endothelioma.
6. Perithelioma.

1. **Fibrosarcoma.**—This variety is the most frequent. It is generally of harder consistency than the round-cell sarcoma, but it may also be soft. Its outer surface is lobulated and its cut surface is grayish white or yellowish white, but it may be of a brownish-red color if the blood supply is very well developed. This form of sarcoma is less malignant than the round-cell sarcoma. Histologically, it does not differ from the picture of fibrosarcoma in general; the cells affect the form of a long spindle in which nuclei are found. Spindle cells alternate with masses of genuine connective tissue; hence the name fibrosarcoma.

2. **Polymorphous-cell Sarcoma.**—This sarcoma is a mixture of spindle, round and pyramidal cells. Giant cells may be present also. In frequency this form of tumor comes next to the spindle-cell sarcoma.

3. **Round-cell Sarcoma.**—The round-cell sarcoma forms a soft, rapidly growing tumor. As it is generally composed of several lobes its outer surface is lobulated. The cut surface is generally white and contains necrotic areas. A white, milky juice exudes. The blood supply of the round-cell sarcoma is generally intensely developed. The cells of this form of sarcoma penetrate between the follicles of the thyroid gland, surround and destroy them entirely (Fig. 22), so that, in last analysis, the microscopic examination of a well-advanced tumor shows

only round-cell sarcoma. No trace of a follicle is found except at the periphery of the tumor, where the folliculi have not been entirely destroyed.

The round-cell sarcoma has two kinds of cells: the small and the large. The small cells are composed of a nucleus with a thin layer of protoplasm. They resemble lymphoid-tissue cells very much. The variety with large round cells contains abundant and granular protoplasm. The nucleus is large and oval. The latter variety is less malignant than the sarcoma with small round cells.

4. **Myxosarcoma.**—Myxosarcoma is a rare tumor and does not differ materially from the fusocellular sarcoma. It is formed by fusiform sarcomatous cells and abundant mucinoid tissue.

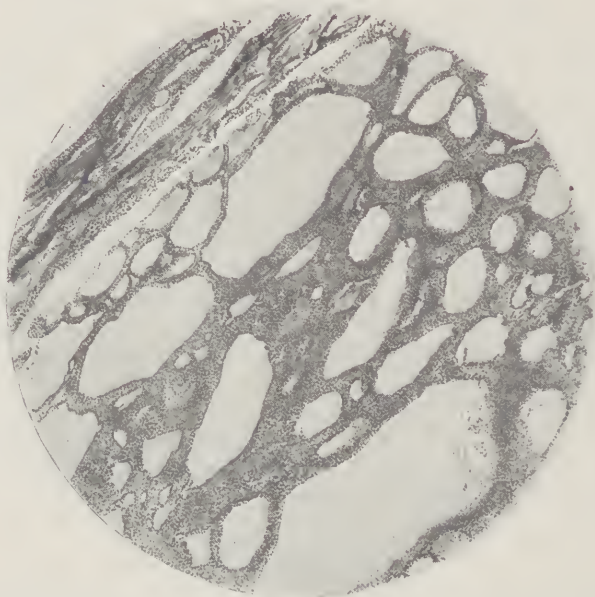


FIG. 22.—Round-cell sarcoma. The small, round sarcomatous cells are seen penetrating between the alveoli; many of them are already about destroyed.  $\times 50$ .

5. **Endothelioma.**—Macroscopically, the endothelioma is sharply outlined; only later when the capsule and neighboring tissues have been invaded by the tumor does it become diffuse in its limits. The surface is more or less coarsely lobulated because the tumor may be composed of one or more nodules of different sizes. Its capsule, more or less thick, is composed of connective tissue in which bloodvessels have been partly obliterated; hence the frequent areas of necrosis found throughout the tumor. The cut surface differs strikingly from the cut surface of other varieties of sarcoma. Connective tissue irregularly disposed forms a framework in which large vascular lacunæ are found containing fluid or coagulated blood (Fig. 23). Fibrin at different stages of organiza-



PLATE IV



Endothelioma.

Endothelial cells of a vascular lacuna. Note enormous dimensions acquired by the endothelium *a*; blood, *b*.  $\times 280$ .



tion is seen forming gray masses which have been called by Langhans "rubber colloid."

The microscopic picture seems to be at first very complicated. This tumor is composed of capillary vessels with a single layer of epithelium. Little by little the epithelium begins to proliferate; the capillary vessels become larger and finally form large vascular lacunæ filled with blood in which the epithelium has acquired enormous dimensions. (Plate IV.) This endothelium may be desquamated, and in places fills entirely the vascular cleft, thus forming solid cellular cords and nests.

In places, large endothelial cells are found containing in their protoplasm one or several red corpuscles undergoing degeneration and finally forming homogeneous little lumps known as *Russell's corpuscles*. This shows the exquisite phagocytic power of endotheliomata.

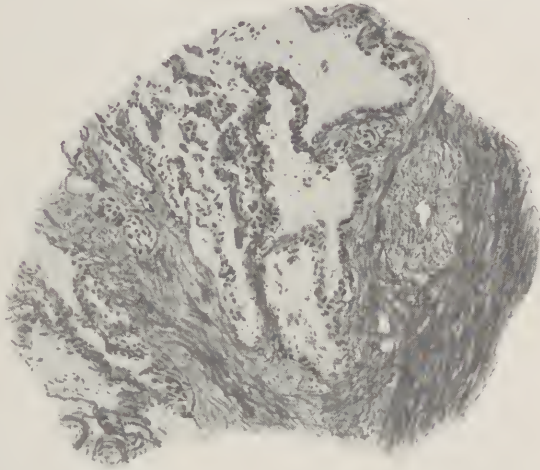


FIG. 23.—Endothelioma. Cavernous portions of the tumor.  $\times 60$ .

The cells are variable in form. They may be polyhedral, round or have a spindle form; protoplasm is more or less abundant and stains heavily with eosin. The nuclei are generally large and contain one or two small corpuscles of chromatin.

Connective formations between the vascular lacunæ are more or less abundant. Metastases take place through the bloodvessels and have the same characteristics as the primary tumor.

6. **Perithelioma.**—Such tumors originate by proliferation of the outermost part of the wall of the bloodvessel. The endothelium is always normal.

The microscopic picture is very typical. It consists of a capillary vessel of more or less large diameter with an absolutely normal endothelium. All around this lumen there are multiple layers of cells forming a thick mantle to the bloodvessels. These mantles may be separated or may fuse together, forming what is called a *plexiform angiosarcoma*.

When fusion between the mantles has not taken place, capillary vessels and thyroid follicles may be found.

The cells may be more or less large and of different forms. The protoplasm stains readily with eosin, and its nucleus contains many small nucleoli of chromatin. Such tumors are generally very hard.

**Combination of Various Forms of Malignant Goiter.**—Carcinoma and sarcoma may occur at the same time in the thyroid gland. This occurrence, however, is exceedingly rare. Such tumors are formed with cells of the carcinomatous and sarcomatous type irregularly mixed together; hence the name *carcinoma sarcomatodes*. Schmorl has seen a carcinoma sarcomatodes occur in a relapsing cancer of the thyroid gland. In the metastases, the sarcomatous type of cell only was found.

### MIXED TUMORS.

These tumors are characterized by their extreme polymorphic aspect, as they contain connective and epithelial tissues, cartilage, bone, etc. They have been called osteochondrosarcoma and osteochondroadenoma, etc. They constitute the first stage in the development of teratomata, with the difference that they do not contain any well-differentiated organ like the latter.

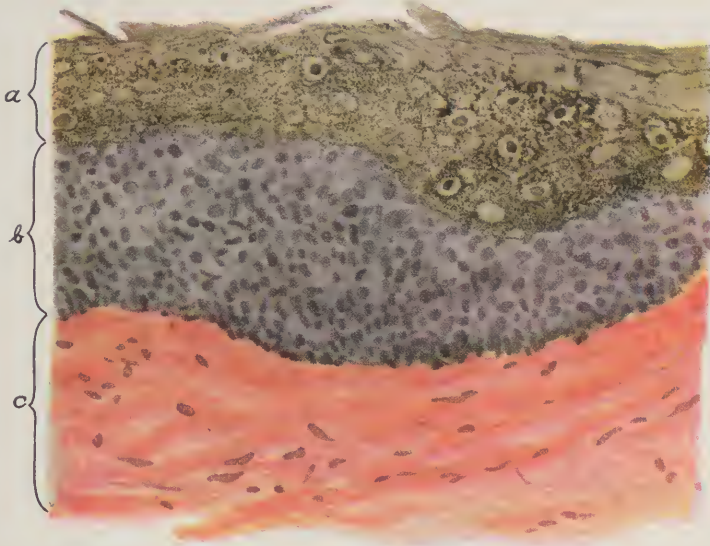
These tumors, although found mostly in old people, seem to be congenital. They undergo malignant degeneration only in old age. Women have them more often than men, and they are found, too, in animals. Their size varies from the size of a fist up to the size of the head of a fetus. Their surface may be smooth, but is more often grossly lobulated. They are firm or hard in consistency, although some portions may be soft. As a rule the tumor has sharp limits except in advanced stages of malignancy. Their walls are often infiltrated with calcareous deposits, so that a saw is necessary to cut them. In the cut surface the cartilaginous and bony formations are found mixed with softer areas formed by sarcomatous or cancerous degeneration. These tumors produce metastases in the lungs, heart, suprarenal bodies, liver, stomach and intestines. The lungs are mostly affected. The histological picture of the metastasis is the same as that of the original tumor; bone, cartilage and other tissues may be found in it.

Histologically, osseous and cartilaginous tissues are found diffusely mixed with thyroid elements; the alveoli may proliferate intensely and their epithelium in places may become cylindrical. Colloid is also present in alveoli.

The most common form of degeneration of connective tissue is the fusocellular sarcomatous type. Blood is supplied by vascular lacunæ whose thin walls will explain easily why hemorrhages are frequent in such tumors.

# PLATE V

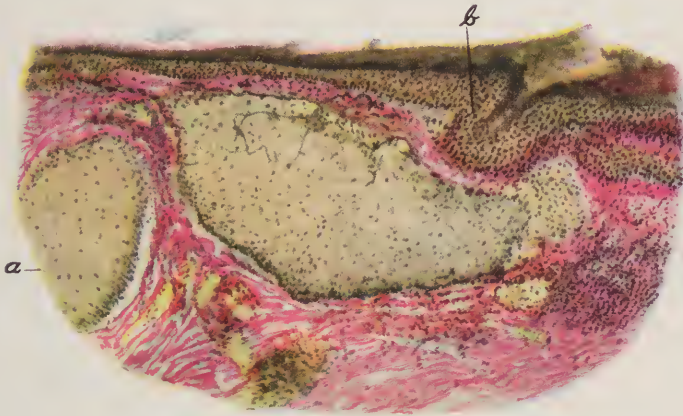
FIG. 1



Dermoid of Thyroid.

Skin with (*a*) stratum corneum; *b*, stratum mucosum; *c*, stratum conjunctivum.  
X 300.

FIG. 2



Dermoid of Thyroid.

*a*, sebaceous glands; *b*, stratum pilosum. X 100.





Hyaline and reticular cartilage are more or less constantly found in mixed tumors of the thyroid. Their distribution throughout the tumor is capricious and does not follow any rule. The osseous elements have not, like normal bones, a lamellous structure; the osseous corpuscles are not as well formed as the normal ones. As a rule the structure of these bony formations affects the spongiform type; the eburneous type is rare. No medulla is found in the trabecules.

Solarno, of Milan, reported in 1914 a case of osteosarcoma developed in the left lobe of the thyroid. The tumor was enucleated but recurred quite rapidly. It was formed, histologically, of sarcomatous and osteoid elements.

The pathogeny of such tumors can be explained by the *theory of metaplasia*; in other words, they are due to an abnormal and incoherent proliferation of normal glandular elements. Such conception is based on indisputable facts of substitution of one tissue by another. For instance, the ossification of a scar tissue in the abdominal wall after a laparotomy is a well-known fact. While assistant to Professor Kocher, I remember that eight to ten months after a median laparotomy for a gastric cancer, we removed a large ossification which had developed in the old scar; histologically, it proved to be ossified connective tissue.

Cohnheim explains the origin of such tumors by the *inclusion theory*. In his judgment some non-differentiated cellular elements of other organs are accidentally mixed and held among the thyroid cells at the time of their embryological formation. For a long time they remain inactive, but in later periods of life, for some unknown reason, they begin to proliferate and develop into these peculiar tumors.

**Dermoids and Teratomata.**—These tumors are exceedingly rare. Three or four cases have been reported in the literature. They represent a step further in the development of mixed tumors. In the latter ones the elements are mixed together without order and are represented by a cellular, non-differentiated mass; whereas in dermoids and teratomata these elements are organized into rudimentary organs as skin, hair and other well-developed tissues. There are only very few cases on record. They may be malignant, or they may not.



FIG. 24.—Dermoid cyst.  
Natural size.

Personally, I came across one benign case (Fig. 24). The dermoid in itself was a very small nodule about the size of a small nut, placed among other colloid nodules. There was no infiltration of the neighboring tissues, and the only feature which attracted my attention was its white, transparent appearance. Microscopically, it proved to be skin with sebaceous and sudoriparous glands. (Plate V, Figs. 1 and 2).

## CHAPTER V.

### INFLAMMATIONS OF THE THYROID.

Inflammations.	1. Bacterial	Acute	<ul style="list-style-type: none"> <li>{ Non-purulent.</li> <li>{ Purulent.</li> <li>{ Syphilis.</li> <li>{ Tuberculosis.</li> <li>{ Ligneous or woody thyroiditis.</li> </ul>
		Chronic.	
	2. Toxic.		
	3. Parasitic.	<ul style="list-style-type: none"> <li>{ <i>Chagas</i> thyroiditis.</li> <li>{ Echinococcus.</li> </ul>	

**History.**—As early as the eighteenth century a number of descriptions of purulent and non-purulent thyroiditis were given by Carron, Walter, Hedenus, Conradi and Bischof. The disease was called by some “cynanche thyroidea” and “angina thyroidea”; it was called by Walter “struma inflammatoria”; Franck called it “thyreophyma acutum,” and Baillie, “inflammatio glandulæ thyroideæ.” Hedenus, Franck and Conradi seem to have realized in their descriptions of the disease that there was a difference between inflammations of a normal thyroid and inflammations of a goiter, as Conradi, in 1824, objected strenuously to the name “struma inflammatoria” applied indifferently to any infectious disease of the thyroid. In 1840, Weitenweber fully appreciated the difference between the two conditions and called inflammation of the normal thyroid “thyreo-adenitis” and inflammation of a goiter “struma inflammatoria.” In 1857, Bauchet published a very complete article on both forms of inflammation. As Conradi did, Bauchet also considered the non-purulent form of thyroiditis as the forerunner of the purulent form. In 1878, Kocher, speaking of the etiology of infectious diseases of the thyroid, made a great step forward in claiming that all inflammations of the thyroid were of a metastatic nature; and the correctness of such views was demonstrated bacteriologically by Tavel in 1892. In 1895, Mygind, dividing thyroiditis into two classes, the “simplex” and the “suppurativa,” claimed that the first one was not always a forerunner of the second, but was in many instances a disease *sui generis*. Ewald, in 1896, although admitting that the thyroiditis simplex might be of “idiopathic or metastatic” origin, did not recognize for it an entity of its own but looked upon the non-suppurative thyroiditis as the forerunner of the purulent form.

The same was done by von Eiselsberg. In 1894, De Quervain, in an eloquent and scientific article, took up this question again and shared entirely Mygind's views. In his judgment the non-purulent thyroiditis is a disease *sui generis*, sharply defined clinically as well as pathologically.

Before discussing these views let us have a clear understanding of the terms we use. We call *thyroiditis* an inflammation of a normal thyroid gland and *strumitis* an inflammation of a goiter, no matter what its variety may be. When we speak of a *primary thyroiditis* or of a *primary strumitis* we mean an inflammation which apparently seems to occur spontaneously in a normal thyroid or in a goiter; nowhere in the organism can a focus be found which might explain the origin of the infecting agent. *Secondary thyroiditis* and *secondary strumitis*, on the other hand, are infections whose infectious agents have been transported metastatically from a well-defined infected focus in the body, as pneumonia, typhoid fever, etc. Strictly speaking, however, there is no such thing as a *primary infection* of the thyroid. If one examines carefully and critically the so-called "primary thyroiditis" or "primary strumitis" it will always be found that the patient was previously predisposed to infection by some gastro-intestinal disturbances, some chronic intoxications, as syphilis, tuberculosis, saturnism, etc. Thyroiditis and strumitis are all of metastatic origin, *ergo, secondary*; nevertheless, we shall preserve these two distinctions for the sake of convenience and clearness.

We distinguish two kinds of thyroiditis, *bacterial* and *toxic*.

**Bacterial Thyroiditis.**—Bacterial thyroiditis is caused by the settlement of the microorganism itself in the thyroid; *toxic thyroiditis* is due to the inflammatory reaction of the thyroid when in contact with chemical poisons or microbic toxins circulating in the blood.

I cannot bring myself to consider with De Quervain and Mygind the non-purulent form of bacterial thyroiditis as a class apart, a disease *sui generis*. The same microorganism, according to its violence on one side and the means of defence of the body on the other, will in one case determine only a non-purulent thyroiditis; whereas in another case it will produce suppuration. Even if a small purulent focus has started, it may not necessarily continue to develop but may regress and finally be absorbed. Such cases will be catalogued as non-purulent thyroiditis, because clinically we have no positive means of distinguishing the purulent from the non-purulent forms in their incipient stage. In that respect very instructive is the case reported by Breuer. His patient, without any apparent cause, was taken suddenly sick with acute thyroiditis developed in the left lobe of the thyroid gland. Swelling, local and referred pains, difficulty in swallowing, fever, etc., were present; in short, the clinical picture was identical with the one of primary non-purulent



thyroiditis. Four or five days afterward everything had subsided, but in the following weeks he began to show symptoms of exophthalmic goiter, and seven months afterward died from the consequences of this disease. A postmortem showed in the left lobe a small encapsulated *abscess* which proved to be of staphylococcus origin. And yet this case had been labelled in good faith and could not be called anything else than "non-purulent thyroiditis."

A bacterial, non-purulent thyroiditis, in my judgment, is only a phase of a process whose last act is suppuration. This suppurative stage may or may not be reached. We have no means to know beforehand, what course a given thyroiditis will take, whether abscess will form or not. This is certainly true in typhoid, diphtheria, puerperal infection, cholera, influenza, pneumonia and erysipelas. Therefore, if we are willing to say that in acute thyroiditis the inflammatory process, according to the virulence of the microörganism and the individual resistance of the patient, may never go further than the non-purulent stage, and that the same process, when conditions of virulence, resistance, etc., are changed, may pass over to the purulent stage, all well and good (the distinction between the non-purulent and the suppurative stage is needed anyway for the sake of clearness in describing the disease); but to make of the non-purulent stage a disease *sui generis* does not seem to me rational. It might be permissible to put under this separate heading the forms of thyroiditis consecutive to infectious diseases whose bacterial etiological factors are still unknown, as in scarlet fever, measles, parotitis, and acute inflammatory rheumatism; these forms of thyroiditis *do not suppurate*. As we do not know if in such circumstances thyroiditis is due to the microbes themselves, too mild to reach the suppurative stage, or to their toxins, it might be more simple and non-committal to regard them for the time being as diseases *sui generis*, but certainly some day there will be more light upon this subject, and I feel confident these forms of acute thyroiditis will be classified as toxic forms of thyroiditis.

According to the foregoing considerations we will admit that bacterial thyroiditis may develop into two stages, the *non-purulent* and the *suppurative stages*.

*Bacterial thyroiditis* may be *parenchymatous* or *interstitial*. In the *parenchymatous form* the epithelial elements are mostly involved, whereas in the *interstitial form* the connective tissue is mostly inflamed. But, as a rule, both forms of thyroiditis are mixed together, one predominating more than the other.

If we should consider a goiter as the result of an infectious process the goiter in itself would then be a thyroiditis, and strumitis would then become only an epiphenomenon of a previous infection. Indeed, one can-



not fail to see there must be a connection between goiter and strumitis. In regions where goiter is endemic, strumitis is mostly found, whereas thyroiditis is rare. The opposite is true of countries free from goiter.

One of the greatest laws which infections seem to follow with predilection is, that they localize preferably on the site of diminished resistance. Now, then, as we know that in all infectious processes of the body the thyroid is put to a very great functional task, no matter whether one considers or does not consider it to be the great laboratory where the products of thyroid secretion are destined to neutralize or render harmless the poisons of metabolism, it is not illogical to admit that after a long illness the gland is in a state of exhaustion and might become an easy prey to infection. When strumitis occurs in cases in which acute infection has apparently not previously existed somewhere in the body, we are then compelled to admit that goitrous degeneration has created a predisposition to infection. Indeed, goiter with its degenerative and hemorrhagic processes forms a suitable "bouillon" for the growth of microorganisms which happen to be wandering in these regions.

We may consequently conclude that a local pathological condition of the thyroid forms a *locus minoris resistentiæ*, and thus may encourage acute inflammation to settle in the thyroid. The mildest degree of local predisposition is found in thyroid parenchymatous hyperplasia, but as soon as thrombosis, hemorrhages, and regressive metamorphoses, as fatty and colloid degeneration, take place, the local predisposition of the tissues for infection is greatly increased. This is so true that typhoid bacilli, in order to be able to produce a thyroiditis, must have a great virulence or they must develop in a gland already degenerated. Roger and Garnier were unable to produce experimental thyroiditis by injecting typhoid bacilli in the thyroid arteries of the normal gland of rabbits. Traumatism also is an etiological factor. Of course, besides local predisposition the virulence of the microorganism is of great importance.

Yet we must say there are in the body very few organs which are less susceptible to metastases of all sorts than the thyroid; for instance, metastases in that gland from malignant tumors are of the utmost rarity; even tuberculosis, which is one of the most common diseases rarely settles in the thyroid. Certainly, this relative immunity must not be an accidental one; very likely, under normal conditions, the thyroid gland has a powerful bactericidal action, capable of warding off infections.

If it is a well-accepted fact that a preëxisting goiter is a predisposing factor of great importance in the etiology of strumitis, what about thyroiditis? Is there, perchance, a small goitrous nodule there also too small to be detected clinically, and which becomes the point where infection sets in? The problem is not easily solved. We really have no

means to decide, *clinically*, when the thyroid ceases to be normal and begins to become pathological. Bassot, in postmortems of pregnant women who died soon after delivery, found the thyroid three or four times larger than normally, and yet in many of these cases the histological picture was one of a normal thyroid gland. De Quervain found that in a gland weighing 50 gm. or more the histological picture may have been one of an absolutely normal thyroid gland, whereas in glands weighing between 20 and 30 gm. unmistakable signs of diffuse colloid degeneration might be seen. Therefore, neither weight nor size is a positive criterion when it comes to deciding whether the thyroid gland is normal or not.

**Etiology.** — Kocher is the first who brought some light into the etiology of thyroiditis. In the farsightedness of his genius, although at the time he did not have bacteriology to support his theoretical views, he claimed that every acute thyroiditis or strumitis was due to metastasis of an infectious agent located somewhere in the organism or originating from the intestinal canal. Later, bacteriological findings proved the correctness of such views.

Thyroiditis and strumitis may occur spontaneously without any apparent cause, or as a complication of another infectious process. They happen especially during convalescence from an acute illness, and are less frequent in chronic cases.

Infection may take place in three different ways: (1) by *contiguity*: an infection localized in the neighborhood, as for instance, in the case of cervical adenitis, may extend gradually over to the thyroid; this mode of infection is more apt to cause a perithyroiditis or a peristrumitis than a genuine thyroiditis or strumitis; however, the fact is possible and has been observed; (2) by *direct inoculation*, as in a puncture with a needle or an injury with a knife; (3) by the *hematogenous route*. As the thyroid has no excretory canal and does not come into contact with a mucous membrane of any sort, if an inflammation sets in, and if the possibility of an infection by direct traumatism or by propagation from the neighboring tissues has been excluded, there remains only one possible way by which the microorganism might have traveled, and that is by the hematogenous route; bacteria thus thrown into the blood current settle in the thyroid.

If an infected focus exists somewhere in the body, thyroiditis or strumitis may be caused by the direct metastasis of the same microorganism causing the primary infection; but it may be caused, too, by a microorganism of an entirely different nature from that of the primary focus. A mixed infection may even be present.

The number of microorganisms incriminated as etiological factors of thyroiditis or strumitis is a very large one. Osteomyelitis and metastatic

meningitis cannot compete with thyroiditis and strumitis in the way of diversity of microorganisms as etiological factors. Thyroiditis and strumitis have been found to follow not only pneumonia, typhoid, tonsillitis, puerperal infections, gastritis, enteritis, pyemia, but also scarlet fever, diphtheria, malaria, influenza, smallpox, measles, cholera, dysentery, mumps and inflammatory rheumatism. All the infections of the gastro-intestinal tract especially, but particularly of the intestine, have been incriminated in the production of thyroiditis. The microbes mostly found in such conditions are the streptococcus, the staphylococcus, the *Bacillus coli* in pure culture or associated with anaërobic organisms. The symbiosis of the latter microorganism with streptococcus is frequently found in gangrenous thyroiditis. Typhoid bacilli are found, too, as etiological factors of thyroiditis and strumitis. Out of 1700 cases of typhoid fever Liebermeister and Hoffmann found 15 cases of thyroiditis and strumitis with six abscesses.

*Pneumococcus* has been found in acute infections of the thyroid following pneumonia, and streptococcus after erysipelas and puerperal infection.

As said before, traumatism may be an adjuvant etiological factor of great importance in thyroiditis. It does not need to be a direct injury of the thyroid, as a puncture with a needle or knife, but indirect injury is sufficient to cause thyroiditis. This is well illustrated in the case of Schöninger, who reported that a girl, aged three years, after being attacked and nearly choked to death, developed an acute thyroiditis. In that case it is well to assume that a hemorrhage was the consequence of the direct traumatism, forming in that way an excellent "bouillon of culture" for bacteria to grow upon. The same explanation holds true in goiter. Schöninger reported another case of a girl who, while lifting a heavy weight, felt a sharp pain in the region of the thyroid, and soon after developed a strumitis. Similar cases of thyroiditis and strumitis were observed, too, by Kocher in men whose profession it was to carry heavy loads on their heads and necks, and in officers of the army whose duty it was to cry out loud orders, while their uniforms fitted their necks tightly. Cold seems to have been in some cases etiologically responsible for thyroiditis.

Thyroid inflammations have been found at every stage of life, from the young child to the old adult. Demme saw a congenital strumitis in a newborn babe, and Berard a strumitis in an old man, aged seventy-five years. A case of mine was in a woman, aged seventy years. But the period of life in which they are most frequently found is between fifteen and sixty years. Women are more often affected than men, and this may be explained by the activity of their sexual apparatus. Each period of their genital life, as puberty, menstruation, pregnancies, the



menopause, is an occasion for congestive reactions in the thyroid, and consequently predisposes to goiter development and infections.

**Pathology.**—In a great majority of cases, inflammation is localized to one lobe while the rest of the gland remains normal, but cases have been reported in which infection extended to both lobes and the isthmus. The isthmus and the pyramidal process are less frequently involved.

In the early stage of the development of the infection, namely, in the non-purulent stage, the capsule is furrowed with distended, partly thrombosed veins; the glandular tissue is extremely congested, dark red, and spangled with punctiform hemorrhages. In places small infarcts are seen. Parenchyma, as well as interstitial connective tissue, is involved. Under the spur of the infection the epithelium begins to proliferate; the cells may increase in size and number to such an extent as to become multistratified and to form papillary projections into the alveolar lumen; at the same time a more or less intense cellular desquamation may take place. The colloid becomes vacuolated, thinner, loses its staining power, and in many alveoli disappears entirely. The lymphatic spaces are distended; cells of connective-tissue origin proliferate; infiltration with leukocytes is more or less marked.

According to De Quervain, besides these elements of connective-tissue origin, *giant cells* are found which should not be confused with tuberculous giant cells. They are seen around very thick, seemingly unabsorbable lumps of colloid, and have very likely a phagocytic action. They are the same ones which are found around foreign bodies, and probably have the same significance.

In the *purulent stage* suppuration takes place in one or more of the small hemorrhagic areas. As observed in pyelonephritis, the gland may become entirely dotted with small abscesses, which may remain independent of each other or may fuse together gradually, forming finally a large purulent collection. In thyroiditis the abscess is never very large. In strumitis its size depends upon the dimensions of the preëxisting goiter, and may attain large dimensions, especially in cystic goiter.

Pus varies in consistency and color. It may be thick or thin, yellow, brown or red, according to the amount of blood which it contains and to the nature of the infecting agent. As a rule it is found serous, brownish and hemorrhagic in streptococcus infection; thick and greenish in pneumococcus infection. The purulent pouches when multiple may communicate or may not. In rare instances gas due to gas-producing organisms is found in the abscess.

**Symptoms.**—The clinical aspect of thyroiditis and strumitis varies with the previous condition of the patient and with the virulence of the microorganisms. Clinically, the types of thyroiditis and strumitis following influenza, typhoid, cholera, inflammatory rheumatism, pneumonia

and erysipelas do not differ so very much one from another. They have about the same intensity, the same course, the same symptomatology. In tonsillitis and malaria they seem to have a milder course.

*Pneumonic thyroiditis*, as a rule, takes place during the defervescing period of pneumonia, evolves mildly, has very little tendency to supuration: if it suppurates, the signs of purulent production are slow to appear. Acute thyroiditis develops rarely during the acute period of pneumonia. However, Vitello's case proves that this is possible, although in his case a mixed infection was present: the diplococcus was associated with other microorganisms.

*Typhic thyroiditis*, too, takes place during the convalescing period, is longer in its evolution, and does not frequently reach the suppurative stage. Out of 15 cases of thyroiditis, Liebermeister found abscess formations 6 times. Geza Galli reported lately a very remarkable case of strumitis developed twenty-one years after the patient had had typhoid fever. The incised abscess proved to be, bacteriologically, a pure culture of typhoid bacilli. The author does not say whether the patient was a typhoid carrier.

*Puerperal thyroiditis* occurs, as a rule, between the tenth and fourteenth day from the beginning of the infection.

As a rule in thyroiditis as well as in strumitis the debut of the disease is very sudden and is frequently accompanied by chills and high fever. The patient complains of pain in the region of the thyroid, with a sensation of constriction of the throat. A deep, continuous and paroxysmic pain, although more or less diffusely distributed over the cervical region, is most marked on the side of the affected lobe. It is exaggerated by pressure and by movements of the head, especially by extension, which compresses the gland between the spinal column and the superficial cervical muscles; therefore in order to relax these muscles the patient holds his head flexed. He does the same thing when swallowing. The pain is also increased by the up-and-down movements of the larynx during the act of swallowing. The pain in swallowing may be so intense as to prevent the patient from taking any nourishment. Shooting pains never fail to be present in the back of the ear, occipital region, shoulder, and occasionally in the lower jaw. These referred pains are an early symptom, and are complained of by the patient long before any swelling in the thyroid is noticed. They are due to the inflammatory irritation of branches of the superficial cervical plexus. The sensation of constriction in the throat is due to mechanical pressure on the esophagus and to peri-esophageal edema. In later stages, especially when infection is localized to both lobes, the windpipe is compressed and may be displaced. As peritracheal inflammation may extend to the mucous membrane of the windpipe and of the larynx, laryngotracheitis accompanied



by coughing spells takes place, thus increasing the dyspneic symptoms, which may become very alarming, because in thyroiditis the patient has not had time, as in simple goiter, to get used to the diminished caliber of the windpipe.

One of the peculiarities of thyroiditis is its liability to cause marked cardiovascular symptoms; tachycardia may be more or less accentuated, heart action being between 120 and 140. What strikes the attention at once is the disproportion between temperature and pulse-rate; the heart action remains rapid even if the temperature is not elevated. This tachycardia becomes more accentuated with physical effort, but may appear without any cause, and is then liable to cause the most annoying cardiac palpitations. It is of thyrotoxic origin. Blood-pressure is lowered and, as in Parisot's case, may be so low as to cause symptoms of collapse, which may become very alarming.

These cardiovascular symptoms follow a parallel curve with the inflammation of the thyroid, reaching their maximum when the phlegmasia is at its highest and gradually diminishing with the retrocession of the inflammation. As a rule they disappear only when the inflammation of the gland has subsided for quite a long time before.

Besides these manifestations, symptoms of less importance may be found, as hoarseness due to involvement of the inferior laryngeal nerve. Sympathetic symptoms are rare. The patient complains of roaring in the ears and vertigo; he is extremely agitated and may become delirious. Nausea and vomiting have been rarely reported and they have been erroneously attributed to pressure on the pneumogastric nerves. They are most likely of thyrotoxic origin.

Fifteen to twenty hours after the debut of the infection a diffuse swelling located between the sternocleidomastoid muscles makes its appearance. It is closely related to the larynx and goes up and down with it during deglutition. In a great many instances the swelling involves one lobe, and in some others it may be found extending over both lobes, one side being more swollen than the other. The isthmus and processus pyramidalis are seldom involved. If the gland was previously absolutely normal the size of the swollen lobe will not exceed that of an egg. Of course, if there was previously a goiter, then the size of the swollen lobe will vary accordingly.

The tumor, especially in early development, is hard in consistency. The veins of the neck are dilated; the patient's face is congested and may even become cyanotic; the region of the thyroid is swollen, hot and tense. In some instances infiltration of the cervical region may become so marked that it is no longer possible to outline the limits of the thyroid; a diffuse, board-like wall covers the entire region of the neck. Palpation must be done very carefully, as it is exceedingly painful and may provoke suffocating spells.

Objective as well as subjective symptoms increase very rapidly. In a few days they reach their maximum. If thyroiditis remains in the non-purulent stage, it usually subsides rapidly and disappears in a few days or in two or three weeks. According to Ewald the non-purulent form is found in 25 per cent of acute inflammations of the thyroid. In some instances, after a period of rapid amelioration, the disease retrocedes more slowly and may be protracted over a period of several weeks. The gland usually recovers its previous normal condition, or a few indurated areas, which in time will be converted into fibrous goiters, may be left as the only living witnesses of the past phlegmasia. Exceptionally, after a remission of a few days, if the infection has been confined to one lobe only, the opposite side may become involved and acute symptoms begin all over again.

But in many instances the infection instead of retroceding, progresses until an abscess is formed. The skin becomes more and more red and swollen until fluctuation becomes manifest. If the abscess is not incised it may open spontaneously outside, leaving a fistula which may last quite a long time—seven years in P. Franck's case. In some instances the abscess may rupture into the trachea and the esophagus. Death is not necessarily the consequence of such an accident, as cases have been reported in which, after spontaneous rupture of the abscess into the trachea, recovery was uneventful. If the abscess fuses downward into the mediastinal space, it causes a diffuse, purulent mediastinitis which is most invariably fatal.

In some rare cases of thyroiditis called by Lebert *thyroiditis desiccans*, a portion of the thyroid gland is found spontaneously severed from the body of the gland, swimming in a fetid, reddish serosity similar to the one found in phlegmon. This glandular sequestrum swims loosely in the purulent cavity; it is often formed by colloid nodules, showing that instead of a thyroiditis we have in reality a strumitis.

Similar cases have been reported by Löwenhardt, Kern, Knuppel, Eulenberg and Middledorff, and considered as *acute massive gangrene* of the thyroid. The special cause of such powerful infections must certainly be looked for in the malignant virulence of microbes such as streptococcus and anaërobic bacilli of putrefaction.

Besides these acute forms of gangrene there are others, less obstreperous, less dangerous *quo ad vitam*, but very much more unpleasant on account of their long duration. They are infections, occurring in old goiters with fibrous or calcareous nodules whose blood supply is precarious, and consequently are soon isolated from the gland and converted into *foreign bodies*. As soon as surgical or spontaneous drainage is established, suppuration does not stop until total elimination of the foreign body has occurred, and this may take months or years.

**Diagnosis.**—Inspection and palpation of the cervical region are so easy there should be no difficulty in making the correct diagnosis. If there is any doubt left, the up-and-down movements of the larynx will clear up the question; the latter symptom is always present except in cases in which inflammation has become so far advanced that a diffuse infiltration extends all over the neck.

Congestion, especially in women, is not an uncommon feature at the time of their menstruation or pregnancy, but in such cases pain, fever and all the other general symptoms found in acute thyroiditis will fail to be present. If a sensation of constriction in the throat, and even respiratory disturbances, are complained of, it will not be difficult to put them in relation with some nervous and hysterical condition of the patient unless a goiter large enough to satisfactorily explain these symptoms should be present.

It may become extremely difficult to differentiate a hemorrhage taking place in a goiter from a strumitis. Spontaneous hemorrhages are very rare in a normal thyroid, whereas they are often seen in goiter. Hemorrhage may take place in a nodule which is so small that the patient is unaware of its presence, and yet such swelling may cause an enlargement of the entire lobe, so that the pathological picture may be mistaken for thyroiditis. The history and development are of great value in differentiating inflammation from hemorrhage. If acute swelling of the thyroid has taken place in connection with some infectious process, the probability will be in favor of thyroiditis; but if the swelling has no relation whatsoever with an infectious process, and perchance has appeared after a physical effort or traumatism, it will be reasonable to admit that we have to deal with a hemorrhage. Local pain and fever, although possibly present in hemorrhage, are less marked than in acute infection, and when present complicate that much more the diagnosis, as in the following case of mine: A young woman, aged eighteen years, had a small goiter for which she was being treated by an osteopath. After severe manipulations of the neck she complained of pain and sensation of constriction in the cervical region. The right lobe, in which goiter was developed, had increased rapidly in size and was very painful to pressure. The temperature was  $101^{\circ}$ ; the skin of the neck was warm but not infiltrated. After three days everything subsided, but the goiter remained a little larger than before. In this case, after some hesitation, I made the diagnosis of hemorrhage in a colloid goiter following traumatism. As the patient did not consent to an operation at any time I never had the opportunity to confirm my diagnosis, although in all probability it was correct.

In conclusion we may say that in hemorrhages, the symptoms reach their climax more rapidly and subside more quickly than in thyroiditis.



To mistake acute thyroiditis for tuberculosis or syphilis is hardly possible. Miliary tuberculosis of the thyroid is only an incident of a more important process, namely, generalized miliary tuberculosis; therefore it has no clinical interest, and is, as a rule, a postmortem finding. Small localized tuberculous foci might be confused with thyroiditis, but their chronic character and the lack of general symptoms will afford the correct diagnosis. The same is true of syphilis.

Differential diagnosis between strumitis and malignant goiter, although, as a rule, without difficulty, is sometimes not easy. For instance, a rapidly growing sarcoma has been mistaken for an acute infection more than once, because in such instances the symptoms have been very much the same. The skin may be warm, red, infiltrated, painful to pressure, and even fever may be present. I saw in Charleston, W. Va., a man, aged forty-five years, a foreigner speaking not a word of English, French, German or Italian, so that it was impossible for me to get any information so far as the history of his case was concerned. In the right lobe was found a large tumor with diffuse limits; very adherent to the neighboring tissues; scarcely sensitive to pressure and firm in consistency. Yet on deep pressure there was a sensation of elasticity. The skin was infiltrated and red; he had no temperature. Although the patient had become very emaciated, he looked to me as being profoundly toxic rather than cachectic, and despite the diagnosis of malignant tumor made by several other physicians, I concluded the patient was suffering from a slow-developing strumitis and advised operation, which later confirmed the correctness of my views.

On account of the difficulty in swallowing, and because of the pain and sensation of constriction in the throat, non-purulent thyroiditis might be confused with tonsillitis, but an intrabuccal examination will settle the matter. An acute cervical adenitis might be mistaken for thyroiditis or strumitis, but their localization and anatomical relations with the other organs of the neck will soon throw some light upon the subject. In the diffuse cervical phlegmon the inflammation is more superficial; the infiltration is more diffuse and deglutition is less painful. In rare instances a mistake might be possible with laryngochondritis.

It is not only of theoretical interest to decide if in a given case we have to deal with thyroiditis or strumitis, but it is also important from the prognostic point of view. Experience shows that thyroiditis is more apt to be non-purulent, whereas strumitis will terminate by suppuration. Consequently, not only the duration but the course of the disease and the dangers connected with it may be predicted to the patient or his family.

In order to decide if we have to deal with a thyroiditis or strumitis the history of the case will be of great assistance, as it will indicate

whether the patient has previously had a goiter or not. If the patient lives in a country where goiter is endemic, not too much stress should be placed upon his answer if negative, as the chances are great that his thyroid might contain a few unobserved goitrous nodules. This is so true that Kocher said he had never seen a case of genuine thyroiditis. All the acute cases which came under his observation were developed in an already degenerated thyroid.

The size of the swelling is of good differential diagnostic value. In thyroiditis the tumor rarely exceeds the size of an egg, whereas in strumitis the size will depend upon the volume of the goiter. In thyroiditis, infection involves from the start the entire lobe. Strumitis, even if developed in a small nodule, remains for a time localized to this nodule; only later the inflammatory processes extend to the entire lobe. If inflammation involves both lobes, the chances are that we have to deal with a thyroiditis, or if one lobe is affected, and after subsiding the inflammatory symptoms appear on the other side, the chances are that we have to deal with a thyroiditis.

**Prognosis.**—The prognosis of acute infection of the thyroid depends very much upon the virulence of the microbes and upon the condition of the patient at the time the infection takes place.

If suppuration does not take place, the inflammatory symptoms subside rapidly; sometimes even small abscesses regress spontaneously, but, as a rule, if suppuration sets in, the process will go on until spontaneous or surgical drainage has taken place. During this period the inflammatory process may endanger the life of the patient on account of the septicemic phenomena due to resorption of infectious materials taking place as long as the abscess under tension has not been opened. It may endanger life on account of pressure symptoms causing asphyxia, and on account of a possible perforation into the trachea, esophagus, pleura, and mediastinal space. The dangers of suffocation cannot be better illustrated than in the case of P. Franck. When he was a mere boy he was taken ill with strumitis. The dyspneic symptoms became so alarming that the life of the child was in danger. The best physician in the neighborhood, called in to see the young patient, declared pompously that "A nerve in the child's neck had been ruptured," and that death was imminent. The mother, who had more medical "horse-sense" than all the medical academy of that time, thought that the swelling in the neck had something to do with the choking of her child. She called in the barber at the corner and told him to make an incision with his razor in the swelling. The barber did so, and at once a stream of pus rolled out. The dyspneic symptoms ceased, and so was saved the life of P. Franck, who at the beginning of the nineteenth century became



a surgeon of great repute. As a result of this incision a fistula remained for seven years before closing spontaneously.

So far as death is concerned, non-purulent thyroiditis is very much less dangerous than the purulent form. According to Robertson's statistics, 12 out of 96 cases died; 54 were non-purulent thyroiditis, with 2 deaths; 41 were purulent, with 9 deaths; 1 was gangrenous, with 1 death. It seems, however, that with our present knowledge of surgery, the death-rate ought to be reduced.

A serious and frequent sequela of thyroiditis is the development of exophthalmic goiter.

**Treatment.**—In non-suppurative thyroiditis the treatment will differ according to the infecting agent; for instance, rheumatic thyroiditis will be amenable to treatment with sodium salicylate; thyroiditis consecutive to malaria will be greatly benefited by quinine; thyroiditis due to influenza will also derive benefit from salicylate. For the other forms of thyroiditis we have no specific remedies; the treatment must be symptomatic. As a rule we might say that in every form of thyroiditis, except the malarial form, salicylate should be used because many of such acute cases seem to be in relation with some rheumatic condition. As non-suppurative thyroiditis subsides spontaneously no surgical interference will have to be considered unless the inflammation should have taken place in a diffusely enlarged parenchymatous or colloid gland causing dyspneic symptoms. In that case the surgeon may be called upon to perform a tracheotomy, or, better, thyroidectomy.

When the abscess is formed, it must be opened and drained, and, by the way, it is not always easy to tell whether the abscess is present or not. Fluctuation, which is really about the only reliable sign betraying the presence of pus, is not always detectable because the abscess may be deeply situated and surrounded by a hard, thick capsule of peristru-mitis, or because small abscesses may be diffusely spread throughout the gland, so that if one should wait for fluctuation to appear before interfering surgically, he might overlook the psychological moment for operation and thus allow his patient to run undue risks so far as complications and death are concerned. On the other hand, one might be so misled as to take a pseudofluctuation for a real one, and on the strength of such findings may be induced to operate, expecting to find an abscess. Great will be his surprise to find only a much-congested gland.

Very suggestive of abscess formation will be the fact that inflammation is no longer localized to the lobe itself, but has extended diffusely to the neighboring tissues. Very suggestive, too, of an abscess formation is the presence of a very hard lobe whose central portion seems to be soft. The blood count and temperature may be of help. In non-

suppurative thyroiditis the temperature climbs gradually, and when it has reached its climax, gradually comes down in lysis, whereas in abscess formations the temperature remains high and takes a septic curve.

It would be a mistake to rely upon an *exploratory puncture* as a means of deciding whether the abscess has formed or not, because if the puncture is negative, it does not mean that pus is not present, but means only that the needle did not strike the purulent pouch or that the pus is too thick to be aspirated. If symptoms are so alarming as to necessitate an immediate operation the exploratory puncture only means precious time lost. If they are not, there will be enough time left to make a correct diagnosis without endangering the life of the patient by an exploratory puncture, because this puncture is by no means a harmless one. It may determine a sudden hemorrhage into the goiter and, consequently, cause severe choking spells in a very short time. Hence the following rule: If at any time one wishes to make an exploratory puncture, everything should be in readiness for an immediate subsequent operation if it should become necessary.

In conclusion we may say that the diagnosis of abscess cannot always be made with certainty, and that it is better to operate a little too soon than too late. If the abscess is still very well encapsulated, and if the infiltration with the neighboring tissues is not such as to render the operation extremely difficult, the removal of the tumor *in toto* is the most feasible thing to do; but if for some reason or another the surgeon must be parsimonious with the thyroid tissue, as in a case of bilateral thyroiditis, incision of the purulent pouch and drainage is the logical procedure. It is nearly impossible to set down hard-and-fast rules, as indications will vary with each given case. Judgment and experience will be the surgeon's best guides.

**Toxic Thyroiditis.**—As we have a toxic hepatitis and a toxic nephritis, so we have also a toxic thyroiditis. It is caused by chemical poisons and bacterial toxins, whereas the bacterial thyroiditis is caused by the microörganism itself. Experimentally, it has been very well demonstrated that chemical poisons such as phosphorus, nitrate of silver, iodine, turpentine and pilocarpine cause a toxic thyroiditis characterized histologically by hyperplasia, degeneration and desquamation of the epithelium and sometimes by increase, but more often diminution or absence of colloid, and more or less marked hyperemia. As a rule leukocyte infiltration is less frequent than in bacterial thyroiditis. In nicotine and lead poisoning no alterations are present. Although mostly absent, swelling in such toxic conditions may be more or less marked; it is a well-known fact that acute iodism may be followed by acute swelling and inflammation of the parotids. The same may be true for the thyroid as in Lublinski's case, in which the thyroid became swollen

and inflamed during treatment with KI. Every symptom subsided after the medicament was discarded.

That hyperthyroidal reaction may follow medication other than iodine is illustrated in a case of an early paretic reported by C. C. Wholey, in 1918. This patient's blood was strongly plus while she also had a mild hyperthyroidism. Antiluetic treatment was urgent. Three daily inunctions of mercury brought about an acute mercurial poisoning with marked aggravation of the hyperthyroidism symptoms, including swelling of the gland. Here, too, we have a toxic thyroiditis.

When once it was found that the thyroid was so susceptible to chemical poisons it was only logical to conclude that bacterial toxins might have the same effect upon that organ, hence the experiment undertaken by Roger and Garnier, Crispino, Torri, De Quervain and others. They found that the introduction of bacterial toxins into the general as well as into the thyroid circulation had on the thyroid about the same influence as the chemical poisons, causing hyperemia, proliferation, and desquamation of the epithelium, diminution or absence of colloid and its increase in the lymphatic vessels. According to De Quervain a pure culture of a virulent microorganism injected into the artery of the thyroid may pass through the thyroid without leaving any marks of its passage, but, on the other hand, may cause disparition of the colloid, desquamation of the epithelium, and the appearance of polynuclear leukocytes in the alveoli.

After these findings it became evident that a step further should be made and that the relations between thyroid and infectious diseases in man should be thoroughly investigated. Sokolow was the first who, in 1896, tried to work out these relations. He found that in acute diseases, fatty degeneration of the follicular epithelium with desquamation took place. Müller in the same year reported about the same findings. In 1900, Roger and Garnier reported the result of the examination of forty thyroid glands which had been taken from patients who had died from measles, scarlet fever, diphtheria, acute gastro-enteritis, typhoid, cerebrospinal meningitis, peritonitis, rabies and smallpox, and in nearly every case they found marked histological changes in the thyroid. Even diffuse hemorrhages were present in three cases. In some instances the epithelium had proliferated to such an extent as to form papillary formations projecting into the alveolar lumen. The cellular protoplasm was found granular, nuclei were swollen and stained with difficulty. Hand in hand with proliferation a cellular desquamation was noticed. The colloid, thin in places, was absolutely absent in others. The interstitial connective tissue showed very little pathological changes except in thyroids of patients who had died from tuberculosis. In such instances the authors found a diffuse sclerosis of the thyroid,



the alveoli being choked by the increased connective tissue. In their opinion this sclerotic process was the result of tuberculous toxins. They concluded that in infectious diseases, according to the gravity and duration of the infectious process, after a period of functional stimulation leading to hyperthyroidism symptoms, the thyroid, injured by persistent and deleterious irritations of toxic nature, may finally be put in a state of more or less complete functional inhibition; hence hypothyroidism. Torri shared the same views.

Kashiwamura, in 1901, relating the results of his investigations on 53 thyroids from patients dead from various infectious diseases, tried to disprove the findings of Roger, Garnier and Torri. He did not find the same typical changes described in the epithelium, colloid and connective tissue, and concluded that, owing to the fact that the physiognomy of the thyroid is already so variable in normal conditions, it would not be safe to draw conclusions derived solely from its histological appearance; in other words, it is difficult to decide what belongs to the normal histology and what belongs to pathology. De Quervain, Crispino, Sarbach, Serrafini, Vitry and Giraud, on the other hand, found that a manifest relation between the thyroid and infectious diseases exists, and according to their researches the pathological changes are mostly in proportion to the severity of the disease. De Quervain, investigating the condition of the thyroid in 45 cases in which the cause of death was tuberculosis, cancer, cardiac, liver and kidney diseases, peritonitis, puerperal infection, diabetes, scarlet fever, smallpox, measles, diphtheria, typhoid, and pneumonia, found changes in the epithelium characterized by proliferation, desquamation, fatty degeneration of the desquamated cells, thinning, diminution or absence of colloid, increased vascularization in the gland *in toto*, and some pathological changes of the connective tissue with, in certain cases, leukocyte infiltration. In patients who died from cancerous cachexia, diabetes, nephritis, Addison's disease, and uremia no pathological changes of the thyroid were detected. Sarbach's conclusions, after investigating 67 cases, were as follows:

1. Acute infections may produce in the thyroid histological alterations, characterized by increase in size and in number of the alveolar cells, their desquamation and degeneration, liquefaction and diminution of the colloid, and hyperemia. The connective tissue remains intact.
2. Alcoholism can determine similar alterations in the gland.
3. Chronic pulmonary tuberculosis produces a sclerosis of the thyroid with secondary atrophy of the alveoli.
4. Nephritis, uremia, cancerous cachexia, and sarcoma do not produce any alterations of the thyroid.



Sefer and Esmonet, treating the epithelium of the thyroid with osmic methods, found that normally the epithelium is exempt from fatty degeneration, whereas in infections and cachectic conditions, as in cancer, leukemia, and tuberculosis, the epithelial elements have undergone a marked fatty degeneration. Finally, Gregor, in 26 thyroids of children who had died of scarlet fever, found, too, the same pathological changes reported by all authors.

Consequently, from all this wide and carefully conducted research work we can safely conclude that the thyroid does not remain indifferent in the presence of the important pathological phenomena taking place in the organism. It reacts more or less constantly to every infectious process by some degree of hyperplasia which is often clinically detectable. It is then known as *Vincent's thyroideal symptom*.

The question arises whether, in a given case, we have to deal with a bacterial thyroiditis or a toxic one, and I must say that the differentiation between the two is certainly not easy. We might say that in toxic thyroiditis, as the entire gland is flooded with toxins, the damages will be diffuse and spread all over the gland. Furthermore, as the toxins are diluted in the blood, their damaging power being diminished, pathological changes, except in severe intoxication, will be more or less mild. Consequently, the immediate clinical symptoms will be much less marked than in bacterial thyroiditis, and swelling of the thyroid may not be present at all, although a slight enlargement may easily escape unnoticed. In that respect the researches of Garnier are extremely interesting. Taking systematically the measurements of the neck in 20 cases of scarlet fever he found that in 11 cases the circumference of the neck was increased from 1 to 2 cm., yet no clinical symptoms were present. Very likely if more attention should be given to this phase of the question we should find that Vincent's thyroideal symptom in infectious diseases is present more often than we think.

If toxic thyroiditis has a less noisy symptomatology and pathology than bacterial thyroiditis, it does not follow that it is a harmless occurrence, as this form of thyroiditis seems preferably to injure the physiological function rather than the anatomical elements of the thyroid. Frequently there is found an acute Graves's disease grafted upon a seemingly innocuous infection, as tonsillitis, etc. Even myxedema has been the consequence of such toxic conditions.

**Tuberculosis of the Thyroid.**—It is classical to say that tuberculosis of the thyroid is rare. Rokitansky, in 1861, denied its existence and Virchow voiced the opinion that no organ in the body is so little predisposed as is the thyroid, that it is of the utmost rarity, and usually the result of tuberculosis of the neighboring structures invading the gland by contiguity. A year later Lebert described the first case. Rindfleisch,

in 1896, Langerhans, in 1902, Schmaus, in 1907, did not mention tuberculosis of the thyroid. Ziegler, in 1902, said that it is not uncommon, that it may occur as a large nodule, and that infection occurs through the hematogenous route. In the same way, Ribbert and Kauffmann believed that tuberculosis of the thyroid occurs mostly in the miliary form of tuberculosis. Gierke, in 1909, believed the same thing. Da Costa regarded tuberculosis of the thyroid as a miliary phenomenon. Lately Arnd, in looking over the literature, found 44 cases which seemed to be undoubtedly of tuberculous origin.

Tuberculous foci occurring in miliary tuberculosis are without interest; they have no entity *per se*, but are only the consequence of a generalized process extended to the entire organism.

*Follicular* tuberculosis of the thyroid, secondary to a primary focus localized in some other organ, is more frequent and better known. Lebert, in 1862, was the first to call attention to it, and since then, other pathologists have studied it. Chiari, in 1878, thinks that it is common in the acute form of tuberculosis, 3 out of 4 cases (What a small number to draw conclusions from!), but rare in the chronic form, 4 out of 96 cases. Fraenkel and some other authors have confirmed these results, which were, however, only postmortem findings.

The *caseous* form of tuberculosis of the thyroid is rare. The first case was published by Bruns, in 1893. It was that of a woman, aged forty-one years, with a large goiter growing rapidly in size. The tumor was hard, painful to pressure, had diffuse limits, and caused shooting pains and dyspnea. Bruns considered the case a malignant one, but was very much surprised at the operation to find only a caseous tuberculous goiter. A few other cases have been reported since, and in conclusion it may be said that caseous tuberculosis in goiter, forms a tumor, more or less hard in consistency, painful to pressure, with diffuse limits and has a tendency to infiltrate neighboring tissue. Diagnosis is very seldom made before the operation.

Localized areas of tuberculosis may be found, too, in a simple goiter; no clinical or pathological symptoms betray their presence, and they are revealed only by a careful microscopic examination. Ruppenner was the first to describe such a condition, and reported 3 cases of colloid goiter in which he was able to detect such tuberculous lesions. Von Werdt, in going over 444 cases of simple goiter, found similar conditions three times. Out of 29 exophthalmic goiters he found 1 with tuberculous areas. Mosiman, in 1917, reported 9 cases of tuberculosis of the thyroid gland. In all these cases diagnosis was made only after the operation and tuberculosis was not suspected in any of the gross specimens after operative removal. Rendleman and Marker, in 1921, reported a case which they regarded as one of primary tuberculosis of the thyroid. The

patient had an enlarged thyroid causing no toxic symptoms. The pre-operative diagnosis made was the one of malignancy. Microscopic examination, however, revealed a diffuse tuberculosis. The goiter was of the fibrous type, showing a diffuse, dense fibrous infiltration and numerous tubercles. Some of the tubercles contained giant cells, but the majority did not. Arnd found 3 cases, Hedinger 10, out of 608 goiters.

The tuberculous lesions are found in the nodular goiter itself or in the normal parenchyma between the nodules. Hedinger thinks that tuberculous lesions in conjunction with goiters are more frequent than is thought, because these lesions, being so small, easily escape attention unless looked for in seriated slides. They are really microscopic findings.

Besides these massive as well as tiny tuberculous lesions, a more or less marked *sclerotic* condition may be encountered in the thyroid, due to a chronic toxic irritation from the tuberculous toxins. In certain instances sclerosis may become so developed that a condition of canceriform appearance known as *woody thyroiditis* follows. The tumor is hard like wood, has diffuse limits, is in the great majority of cases painful to pressure, and rapidly causes marked dyspneic symptoms. Its true origin, as a rule, is not recognized and the diagnosis of malignant tumor is nearly always made.

In most of the cases reported the presence of tubercle bacilli, without which an absolute diagnosis of tuberculosis cannot be made, was not observed. The diagnosis was made solely upon the microscopic and histological picture, which in the majority of cases is sufficient to warrant such a diagnosis.

Some authors seem to think there is an indisputable relation between goiter, Basedow's disease, and tuberculosis. The impression gained from the small amount of experimental work along this line is that the thyroid is peculiarly resistant to tuberculous infections. Pinoy, injecting guinea-pigs with tuberculous bacilli, found only once the thyroid gland infected with tuberculosis; therefore, he concluded that the thyroid, as well as the pancreas and other glands, show a special resistance to tuberculous bacilli. In 1900, Torri injected an emulsion of tubercle bacilli directly into the thyroid artery of dogs. The corresponding lobe became markedly affected with tubercle bacilli, while the lobe on the other side showed only a marked proliferation of the epithelium. No tubercle bacilli could be demonstrated in the colloid material of the glands removed ten days after, and because of the fact that the microorganisms did increase on adding thyroid extract to the culture media, he was led to believe that the colloid destroyed the tubercle bacilli.

Torrin and Tomellini, on the other hand, injecting directly into the thyroid artery an emulsion of tubercle bacilli, found in each case the corresponding lobe infiltrated with tuberculosis. Shimodaira repeated

the same experiment, but in one series injected heavy doses of tubercle bacilli and in the other series small doses. He found that in the first series of experiments the gland was infected with tubercle bacilli while in the other it was not. Therefore, he concluded that unless overpowered by numbers the thyroid gland shows a special resistance to tubercle bacilli.

Many seem to believe that the thyroid has an immunizing influence against tuberculosis, not only for the gland itself but also for the entire organism. Morin, working in a sanitarium for tuberculosis in Leysin, after examining several hundred tuberculous patients, came to the conclusion that the disease undergoes a more acute and malignant course in cases in which the thyroid is atrophied; whereas in cases in which a thyroid hypertrophy or even a goiter exists, the course of the disease is milder. I do not know how far these conclusions are justified, but it is, nevertheless, a fact that myxedematous patients are easily the prey of tuberculosis, as shown by McKenzie, who out of 71 cases of myxedema found that 20 were tuberculous. This, however, could be explained by the retarded metabolism and the diminished resistance of the patients.

Costa goes so far as to pretend there is an etiological relation between goiter and tuberculosis. Goiter, in his judgment, is due to the reaction of the gland against tuberculous toxins. If he meant that the thyroid *may* react to tuberculous toxins by toxic thyroiditis, all well and good; otherwise he must have been the victim of coincidences, because we see too many cases of goiter in which no tuberculous lesions are found, and *vice versa*. Let us remember that Hedinger found only 10 microscopic tuberculosis cases out of 608 cases.

Goiter and tuberculosis are among the most common diseases, and if there were any etiological relation between the two, it seems that this fact could be easily demonstrated, as thousands of cases are seen each year. In the many thousands of cases of goiter which I have seen, pathologically as well as clinically, tuberculosis associated with simple goiter was only an accidental occurrence.

On the other hand, the relation of cause to effect between Basedow's disease and tuberculosis cannot be denied. It is not uncommon to find a Graves's disease grafted upon a case of early tuberculosis; even marked exophthalmic symptoms may develop in the course of advanced tuberculosis. From the cases I have seen, however, I could not say that tuberculosis was of more frequent occurrence in the history of my Basedow's patients than any other acute illnesses, as typhoid, pneumonia, tonsillitis, etc. I shall take up again these relations between acute infectious diseases and Graves's disease in the chapter on the Etiology of Thyrotoxic Goiter.



**Syphilis of the Thyroid.**—Although Falta in his text-book claims that the thyroid gland is involved in more than 50 or 60 per cent of the cases of acute syphilis, little is known about the behavior of the thyroid in secondary syphilis. If all we do know about this is the concomitant thyrotoxicosis occurring in a few cases of secondary syphilis, the first condition being apparently dependent upon the second, as shown by specific treatment, we have, nevertheless, a little more specific data concerning the tertiary form of syphilis of the thyroid. Berard, Favre and Savy have made important contributions to this subject.

Syphilitic gumma of the thyroid is rare and only a comparatively few authenticated cases of this condition have been reported in the literature. Its existence has not long been recognized since Lancereaux, in 1868, said, "We do not know of any case which gives evidence of gummatous deposits in the substance of the thyroid gland."

The earliest mention of gummatous lesions of the thyroid was made by Demme, in 1878, when he reported 3 cases of syphilitic gumma of the thyroid in infants. In such cases the gummata were varied in size, were of grayish or yellowish color and sharply outlined, not unlike malignant nodules.

In 1884, Barth and Gombault reported a case of a syphilitic gumma of the thyroid confirmed by histological examination.

In 1887, Fraenkel reported a case of a woman in whom gummatous syphilis of the thyroid was present. There was at the same time syphilitic involvement of the liver and right kidney.

In 1889, Garnier described syphilitic ulcerations of the thyroid in 5 newborn, characterized by interstitial sclerosis and alveolar atrophy.

In 1891, Engel-Reimers observed thyroid enlargement 86 times in a series of 152 cases of syphilitic females and 44 times in a series of 98 syphilitic patients. The involvement occurred in the lobes and left the isthmus more or less intact. These observations were made during the secondary period of syphilis. The enlargement lasted about a year or so and then gradually disappeared.

If we remember that infections of all sorts act electively upon the thyroid, thus causing a toxic thyroiditis, I do not know how far we are justified in considering the cases reported by Engel-Reimers and Lockwood as cases of true syphilitic thyroiditis. To be sure, they are in direct relation to the general syphilitic infection but no more so than the toxic thyroiditis observed in typhoid, tonsillitis, etc.

In 1892, Kohler reported a case of tertiary syphilis in the thyroid of a woman which responded to antisypilitic treatment very readily.

In 1894, Pospelow reported a case of syphilitic gumma of the thyroid which responded rapidly to antisypilitic treatment. The patient was suffering at the same time from diabetes, which was also controlled by mercury and iodides.

In 1895, Lockwood observed 5 cases of early enlargement of the thyroid in women during the secondary period of syphilis. They were all of young women and all were accompanied by general lymphatic involvement.

In 1896, Küttner reported 2 cases of carcinoma of the thyroid; both were operated, and later proved to be gummatous syphilis of the gland. The first case was of a man, aged twenty-seven years, who had, when seen, considerable difficulty in breathing. The right lobe of the thyroid showed a swelling the size of a fist, was very hard and seemed apparently cemented to the tissues of the neck. This tumor was partly retrosternal and had displaced the windpipe toward the left side. The left lobe was enlarged, too, but did not seem to show the same pathological changes as the right one, inasmuch as it was soft and mobile. The clinical diagnosis of carcinoma was made and the patient subjected to operation. The surgical difficulties, however, were so great that the operation was finally abandoned and a small piece of tissue removed for microscopic examination, which showed that the tumor was not malignant, but rather of luetic nature. Antisyphilitic treatment was immediately instituted and the patient was cured. The second case was that of a woman, aged thirty-nine years, who showed a fist-sized swelling of the thyroid and complained of difficult breathing. The tumor was somewhat mobile, very hard, and nodular in surface. Here, too, a diagnosis of carcinoma was made and a left lobectomy performed. Later, histological examination of the specimen showed that it was a gummatous syphilis of the thyroid. The diagnosis was confirmed by the fact that the patient came back later with a luetic ulceration of the soft palate and that she responded to the antiluetic treatment very readily.

In 1897, Bruce Clarke reported a gumma of the thyroid extending from the hyoid bone to the sternum. There was at the same time a typical "punched-out" gummatous ulceration of the skin over the tumor. The patient had been suffering previously from numerous gummatous ulcerations of all parts of the body. When seen by Clarke the patient had great difficulty in breathing and tracheotomy became necessary, but finally the patient recovered after antiluetic treatment.

Simonton, in 1898, reported 5 cases. The first was that of a man, aged twenty-nine years, with marked symptoms of hyperthyroidism, exophthalmos, tachycardia 150, marked tremor, loss of flesh, etc., Wassermann two plus. Three weeks after salvarsan had been given intravenously the thyroid gland was normal, pulse 94, and the tremor scarcely noticeable. One year after the patient was absolutely cured.

The second case was that of a woman, aged twenty years, with marked exophthalmos, loss of weight, tremor, protrusion of the eyeballs, tachycardia 130, Wassermann four plus. The patient was pregnant two

months. Antiluetic treatment was kept up during her whole pregnancy and after delivery the patient gained in weight and improved considerably. No absolute cure, however, was effected.

The third case was that of a woman, aged forty-two years, with a goiter developed in the right lobe, soft and "doughy" in feeling. She complained of shortness of breath, difficulty in swallowing, especially when lying down, and hoarseness. Wassermann was four plus. Salvarsan was given intravenously and repeated in seven days. The patient improved very remarkably and after six months was free from all symptoms, although the gland remained slightly enlarged.

The fourth case was that of a colored woman, aged nineteen years, with a large colloid goiter causing pressure symptoms. Wassermann four plus. No treatment was instituted in this case and the patient was taken home. The mere presence of a four plus Wassermann in a case of large nodular goiter is not enough to justify Simonton's claim that this was of luetic origin. This case should have been left out entirely from his report.

The fifth case was that of a woman, aged twenty-nine years, having had five miscarriages and two stillbirths covered with syphilis. Wassermann two plus. She had a large goiter causing marked pressure symptoms, dyspnea, hoarseness, and difficulty in swallowing. She was also pregnant. Specific treatment resulted in the reduction of the size of the gland and in partial alleviation of the symptoms after the birth of the child. Here, again, the diagnosis of syphilitic goiter must be regarded as doubtful, since the antiluetic treatment did not relieve the patient entirely from her goiter. Most likely the enlargement of the goiter and the pressure symptoms were caused by her pregnancy, since soon after childbirth, as is often the case in non-luetic patients, the congestion of the goiter disappeared and caused the benefit experienced by the patient.

In 1900, Wermann reported the case of a man, aged twenty-four years, with a symmetrical swelling of the thyroid gland, soft, painless to pressure, and symptomless. As the case responded very readily to antiluetic treatment, the patient being unquestionably syphilitic, Wermann thinks he had to deal with a case of syphilis of the thyroid.

In 1906, Mendel reported 3 cases in women, 1 in a girl, aged twelve years, who developed a very large goiter increasing rapidly, hard, nodular and developed in the right lobe. Tracheotomy had to be performed, but death ensued. Syphilitic involvement of the spleen and liver were demonstrated. The second case was one of a woman, aged thirty-eight years, who had a goiter developed in the left lobe, which responded very readily to the iodide treatment. The third case was a woman, aged sixty-three years, who developed a rapidly growing tumor in the thyroid, causing marked dysphagia and dyspnea, and when seen the patient was

considered as inoperable. Antiluetic treatment was instituted and the patient cured. However, six weeks later, after having been discharged as cured, she returned with a malignant tumor which progressed very rapidly and caused death.

In 1908, D'Arcy Power reported the case of a syphilitic man, aged fifty-three years, who had a goiter developed in the right lobe. It was hard, smooth in surface, sharply outlined, was not attached to the surrounding structures, did not move up and down when swallowing and gave no pain. Complete recovery followed one month's treatment with iodide of potassium and ammonium carbonate.

In 1910, Davis reviewed the literature of syphilis of the thyroid and reported a personal case. The patient was a man whose age was not given and who gave an undoubted history of syphilis. The patient, who had been admitted to the Cook County Hospital, Chicago, complained of hoarseness, great inspiratory dyspnea, and pain on swallowing. The condition became so alarming that a tracheotomy had to be done. The patient died soon after. Autopsy showed a gumma of the thyroid which was probably primary in the perichondrium of the cartilages of the larynx and had secondarily invaded the right lobe of the thyroid. The histological examination showed a gumma with diffuse inflammatory infiltration between the thyroid vesicles adjacent to the gumma.

In 1911, Sebilleau reported the case of a woman, aged twenty-eight years, with a goiter causing dyspneic symptoms and in which diagnosis of malignancy was made. A thyroidectomy was performed in order to alleviate the symptoms, but could not be completely carried out as the tumor was markedly adherent to the windpipe. Antiluetic treatment promptly cured the patient. He reported another case, that of a man who presented about the same symptoms as the woman just mentioned, likewise in whom the goiter seemed to be malignant and who was cured by antiluetic treatment.

In 1912, Poncet and Leriche reported the case of a woman who had goiter in the right lobe. It was hard, had a wooden consistency, and infiltrated the neighboring tissues. Dyspnea was very marked. The tumor disappeared after treatment with mercury, iodides and salvarsan.

In 1914, Clark reported the case of undoubted involvement of the thyroid in a congenital syphilitic. The patient was a woman, aged twenty-four years, who had suffered from epileptic fits when she was twelve years of age. When seen by the author the patient had a very severe exophthalmic goiter with palpitation and tachycardia and violent attacks of nervousness. The ocular symptoms were only faintly outlined. About a year afterward, the patient's condition became so severe that she became unconscious with each attack. Her pulse went up to 200; she had paralyzed sphincters, and continuous vomiting lasting for a



fortnight. Owing to the past history of epileptic fits when she was twelve years of age, and owing to her "Olympic forehead" the *cranium natiforme*, a Wassermann was made in both the patient and her mother. Both were markedly positive. Mercurial inunctions, epinephrin (1 to 1000 solution, 20 drops three times day) resulted in a rapid cessation of the vomiting and in two days the patient had recovered consciousness. Eight days after, the patient was very much better, so that the mercurial inunctions, aided with salvarsan injections, resulted in complete cure two months after. A year later, however, the same train of symptoms reappeared, but was again controlled readily by the antiluetic treatment.

In 1916, Loyd Thompson reported the case of a man, aged seventy-two years, who was syphilitic, and who showed a goiter developed in the right lobe, causing marked toxic symptoms such as tremor, palpitation, exophthalmos, etc. Although the Wassermann was markedly positive, six weeks after antiluetic treatment the goiter had almost entirely disappeared.

In 1918, Senear reported the case of a man who denied any syphilitic infection, but who, seven years prior to being seen by Senear, had suffered from loss of appetite, general weakness, and from a number of reddish sores covered with whitish membrane in the mouth. These sores persisted for eight months, new ones appearing as the older ones disappeared. The appearance of the thyroid tumor was preceded by a swelling over the upper part of the sternum, which finally ulcerated and was curetted by a physician. No anesthesia was used; the operation was painless. Two months after, the patient was operated again; the ulceration healed but only to reappear, not only on the sternum but also in the left sternoclavicular joint while purulent sinuses also made their appearance. The thyroid tumor was very hard and increased rapidly in size. Probing of the sinuses led into the thyroid. The swelling of the thyroid was about the size of a hen's egg. Numerous cervical lymph nodes were present. Roentgen-ray examination of the lungs revealed no sign of tuberculosis and fluoroscopic examination showed that the esophagus and windpipe were normal. Since Wassermann was reported to be four plus, the patient was submitted to antiluetic treatment with mercury, iodides and salvarsan. The patient promptly recovered. No microscopic examination of the specimen could be made.

These constitute about all the cases recorded in the literature. As may be seen by the study of them, the diagnosis of syphilis of the thyroid is not certain by any means in all, but taking the antiluetic treatment as the criterion, one feels warranted in considering most of these cases as true syphilis of the thyroid.

Syphilis of the thyroid occurs both as an early and late manifestation. It seems to be more frequently found in women than in men and may occur at any age, no matter if the syphilis is congenital or acquired.

The histological picture resembles greatly the one of tuberculosis of the gland. There is an infiltration of round and epithelioid cells; formation of fibrous tissues and giant-cell formation with proliferating endarteritis reaching sometimes the stage of obliteration. It is not always an easy matter to differentiate a diffuse syphilitic thyroiditis from a diffuse tuberculous thyroiditis, inasmuch as oftentimes the histological picture of both conditions is very similar. If one is able to demonstrate the presence of tubercle bacilli or the *Treponema pallidum* then the diagnosis becomes certain, but in a great many instances this is not possible and one has to rely upon the course of the disease, the past history of the patient, the laboratory findings, and especially upon the influence of the antiluetic treatment.

Clinically, syphilis of the thyroid can be suspected in the secondary stage of the disease when a diffuse enlargement of the thyroid occurs at the time of the secondary stage of the lues. It constitutes then a toxic luetic thyroiditis. In the tertiary period it usually forms a nodular tumor, firm or hard, sometimes well outlined, sometimes smooth with diffuse limits, thus closely simulating a malignant tumor. Pain is usually absent. Pressure symptoms are sometimes very marked and may become alarming.

As said above, diagnosis rests upon the history, laboratory findings, and improvement with specific treatment. It would be a mistake, however, always to consider thyroid enlargement and a positive Wassermann as being etiologically interrelated. If one enlarged thyroid disappears because of some antiluetic treatment, it does not necessarily follow that the condition had developed on a syphilitic basis, especially if iodides had been used in the antisiphilitic treatment.

Since in the above reported cases, we find that syphilis of the thyroid has often been mistaken for malignancy, it follows that whenever diagnosis of malignancy is made, the possibility of syphilis should be borne in mind and that every measure available to detect it be employed.

**Woody Thyroiditis.**—It was Riedel who, in 1896, first described a form of thyroiditis which he called “eisenharte Strumitis,” or “iron-hard strumitis.” Riedel’s patient was a man, aged forty-two years, who had a tumor, developed in the thyroid, extremely immobile and causing alarming dyspneic symptoms. He diagnosed it as a cancer of the thyroid and attempted the removal of the tumor, but at the operation the difficulties were so great, the adhesions with the neighboring tissues so intense, that a radical operation had to be given up. He, however, removed a piece of the tumor the size of a walnut and to his great surprise after a few months the patient was entirely cured. Microscopically, no malignant elements were found; the whole thing was simply the picture of a chronic inflammation. On account of the

extremely hard consistency of the tumor, Riedel called it "eisenharte Strumitis." In the same year Cordua, of Hamburg, reported a similar case. In 1898, Jeannel, of Toulouse, reported a case in which he made a diagnosis of cancer of the thyroid; later, it proved to be a case of "eisenharte Strumitis." In 1901, Ricard reported a similar case in which the diagnosis of cancer of the thyroid had been made and which proved to be a case of "woody thyroiditis." Silatschek, of Innsbruck, and Spannaus, of Breslau, reported lately similar cases.

This form of thyroiditis, called by Riedel "eisenharte Strumitis," or "iron-hard strumitis," and by Delore and Alamartine "La thyroidite ligneuse." "woody thyroiditis," has always been mistaken for a malignant tumor, and yet between these two forms of disease the clinical differences are such that a differential diagnosis can often be made. First of all, the woody thyroiditis is found in younger people, that is, those between thirty and forty years of age. Men are more often afflicted with it than women. The disease progresses extremely rapidly, in a few weeks or months. The region of the thyroid is painful and shooting pains are intense. One of the earliest symptoms is dyspnea, which may become so rapidly alarming that death seems imminent, and in many instances tracheotomy is the only salvation. The dyspneic symptoms are due to the fact that the trachea is compressed between the lobes of the inflamed thyroid. The trachea is not displaced unless there has been a goiter previously. Pressure symptoms on the inferior laryngeal nerve show up early. The inflammation extends over the entire gland and seems to occur more frequently in normal thyroids than in goiter. Like a drop of oil, it spreads and infiltrates all the organs found between the superficial and prevertebral fasciæ, thus forming a mass in which everything has become solidified: thyroid, trachea, esophagus, neurovascular cords, sternocleidomastoid muscles and muscles of the subhyoid triangle all form only one mass. Vainly, one would try to find in it a plane of cleavage. The tumor is absolutely hard like iron or wood, hence its name. Its surface is smooth, being irregular only when a goiter existed previously. The larynx, immobilized by the diffuse infiltration, does not go up or down with deglutition. The cervical lymphatic glands are very seldom involved. The common carotid is lost in the midst of the infiltration, whereas in a cancer of the thyroid, especially if there has been a previous goiter, it is displaced backward.

All these symptoms taken together give to the disease a physiognomy which differs from the one of malignant tumors. The extreme hardness, its regularity of surface, its marked diffuseness of limits, the involvement of the gland *in toto* will remind one more of a woody thyroiditis than of a cancer of the thyroid, especially if the disease is found in a young individual, and if it has developed rapidly and caused early dyspneic symptoms, entirely out of proportion to the size of the tumor.



Pathologically, the gland is transformed into a fibrous, whitish, extremely hard mass. If a goiter has existed previously, it is embedded in the fibrous mass. The cut surface is dry and no juice can be expressed, as can be done in cancer. Histologically, the parenchyma is choked by sclerotic connective tissue of interstitial and capsular origin so abundant that alveoli, in places, have disappeared; there is no abscess nor any tendency to suppuration. In the remaining alveoli, desquamation and either thinning or absence of the colloid is present.

In such cases the idea of scirrhus must be soon discarded, as spontaneous healing has been observed, and a complete cure without relapse followed partial extirpation. Fibromata of the thyroid have not the same anatomical and clinical aspect either; they are encapsulated without tendency to infiltration.

As a rule the disease affects individuals who have been in excellent health previously, with no typhoid, pneumonia, or other infectious disease as a preliminary stage. In some instances, it is true, tuberculosis and syphilis have been found as a concomitant complication, so that they might be considered as an etiological factor; but the fact remains that cases of woody thyroiditis, where apparent concomitant infection could be discovered, do exist.

This fibrous, sclerotic process is not peculiar to the thyroid only, but had also been found by Riedel in the pancreas and by Mikulicz and Küttner in the submaxillary and lacrymal glands. The same sclerotic process is known, too, in the digestive apparatus, especially in the stomach and gall-bladder. I remember finding in a postmortem a stomach which had seemingly undergone the same kind of sclerotic degeneration as the one described above in the thyroid, and which is known as the "leather-bottle" stomach. The stomach was transformed into a canal about 40 cm. in length, 10 to 12 cm. in width in the cardiac region, and 6 to 8 cm. in the pyloric region. This canal was extremely hard, its walls were thick, and all the epigastric region was diffusely involved by the same sclerotic condition—no metastases of any kind; no ulcerations of the mucous membrane of the stomach. Macroscopically, I made the diagnosis of "linitis plastica," which was considered at the time as a peculiar form of malignancy, but histologically it proved to be a chronic inflammation.

Bacteriologically, nothing has been found to enlighten us on this subject. Mycosis, and especially actinomycosis, might be incriminated in some cases.

In view of the extreme diffuseness of the lesions, surgical treatment which intends to be radical is extremely dangerous, as extirpation cannot be complete without sacrificing important organs as the common carotids, vagus nerve, and the jugular veins. On the other hand, infiltra-



tion of the walls of these vessels makes the attempt dangerous as they are very friable; ligatures cut through as if in butter. If the dyspneic symptoms become so alarming as to endanger the life of the patient, the best treatment is a cuneiform resection of the isthmus in order to liberate the trachea from its compressing ring. If an operation is decided upon, then, according to Delore and Alamartine, an excision of a small portion of the tumor seems to be sufficient to assure complete recovery. Iodide of potash is an excellent adjuvant, and x-ray treatment seems to be, according to Silatschek and Barjon, specific for this disease. If syphilis is suspected, an intense antisyphilitic treatment should be started at once.

**Parasitic Thyroiditis.**—In 1907, Chagas, working in the Institute of Manghuinos in Rio de Janeiro, discovered a new parasite which he called "*Schizotrypanum cruzi*" in honor of his chief, Oswald Cruz. According to Chagas this living organism causes a parasitic thyroiditis, accompanied by the most severe symptoms, and is very often fatal. The geographical distribution of this disease is not entirely worked out. It is found in Brazil, especially in the State of Minas Geraes. It is transmitted to human beings and to domestic animals by the bite of a hematophagus insect, the "*Conorhinus megistus*." This hemipterous insect lives in the cracks of windows and walls of old huts; it is not found in new houses, consequently the disease is most prevalent among the poorer class of people.

The insect bites during sleep. Its bite is absolutely painless and does not cause any inflammatory reaction. It is not uncommon to see a dozen or more of these insects biting at the same time a sleeping infant without waking it. The parasite is found in the blood under different forms, according to the stage of its evolution. It can be cultivated on blood agar. The period of incubation after its bite is about ten days. According to Brumpt, other insects can also act as hosts, especially the bed-bug (*Cimex lectularius*), the excreta of which are highly infectious.

Tejera claims that the *trypanosome thyroiditis* as described by Chagas, prevails also in Venezuela, but that it is transmitted by a different insect from the one responsible for it in Brazil, namely, the *Conorhinus megistus*, since the latter does not seem to be found in Venezuela. The bug responsible for the transmission of the disease in Venezuela is the *Rhodnius prolixus*.

These insects naturally harbor the *Schizotrypanum cruzi*. They are called by various names, such as pito, chupon, quipito, chinchede monto, and chipo, are night-biting and belong to the *reduvidæ* family.

Parasitic thyroiditis may be acute or chronic. The acute form is found mostly in children under one year of age. The thyroid is swollen,

skin is infiltrated not only in the neck but over the face, and a crepitus on pressure is present. Fever is persistently high,  $103^{\circ}$ , with only slight morning remissions. Cervical glands, spleen, and liver are enlarged. The disease lasts about fifteen to thirty days, and terminates, as a rule, in death. Only exceptionally does it take a chronic course in very young children.

The chronic form is found in older and more resistant children and in adults. If the disease does not terminate fatally, it lapses into a chronic form characterized by goiter, often of very large size, and symptoms due to partial or total loss of the thyroid function dominate the scene. According to the degree of thyroid disturbance the symptoms may be slight, moderate, or very pronounced. It is possible, therefore, to meet with cases which are practically indistinguishable from the usual type of goitrous individuals seen in endemic localities in Europe. It is impossible to distinguish such cases from the true endemic goiter by blood examination, since the trypanosoma, which is said to cause the goiter, disappears from the blood after the acute symptoms have subsided; the true infectious origin of this goiter can be ascertained experimentally by inoculation methods.

Chagas described five different forms which the disease may take:

1. The pseudomyxedematous form: the thyroid is enlarged, the enlargement being confined, as a rule, to one lobe only; the skin shows a mucoid infiltration and has a bronze color, similar to the color characteristic of Addison's disease; irregular and intermittent fever is present.
2. The myxedematous form: symptoms of hypothyroidism are extremely marked.
3. The cardiac form: found mostly in adults and characterized by myocarditis, arrhythmia, and bradycardia.
4. The nervous form: caused by the localization of parasites in the central nervous system; spasmodic motory disturbances are frequently seen in that form.
5. The subacute form: characterized by periods of exacerbation alternating with periods of remission; the prognosis of this form is usually bad.

Postmortem shows enlargement of the thyroid and of the cervical glands; cardiac hypertrophy with a pericardiac, pleuritic, peritonic, serous exudate is frequent. Liver, spleen, and suprarenal bodies are enlarged. Histologically, what dominates in both forms, acute and chronic, is sclerosis due to an exaggerated development of connective tissue. The alveoli are choked and atrophied. In the acute forms, proliferation and desquamation of the epithelium, thinning or absence of the colloid, hyperemia, leukocyte infiltration, in short, the same lesions found in all the other forms of acute thyroiditis are present. In

*chronic cases* the connective tissue is very abundant and cysts in size more or less variable are found in great number. The same inflammatory reactions and cystic formations can be found in the myocardium, muscles, nerves, testicles, ovaries, cortex cerebri, etc.

In the acute form, as the parasites are numerous, a single drop of blood taken from the finger or lobule of the ear will suffice to show the presence of the parasite when colored by the Giemsa method. In the chronic form, 5 to 10 cc of blood injected into the vein of a dog, monkey, or cat will kill the animal after a certain period of time: the schizogonic form of the parasite will then be found in the lungs.

Most significant analogies between what Chagas calls the endemic Brazilian goiter in its chronic form and our own endemic goiter cannot be denied. In both cases there exists the chronic enlargement of the thyroid gland with its accompanying conditions of cretinism and myxedema. Beyond doubt the Brazilian infection is much more severe and the mode of infection and infectious agent totally different, but these conditions do not change the fact that a chronic goiter is developed from an infectious basis. This is, in my judgment, a very strong argument in favor of the infectious origin of our endemic goiter.

**Hydatid Cyst of the Thyroid.**—*Hydatid cysts* of the thyroid are extremely rare. L. A. Landiver went over the literature and found 29 cases, to which he adds 2 of his own. The hexacantic infection takes place through the hematogenous route. Direct inoculation occurs only accidentally as in Minert's case—there the cervical wound was licked by a dog.

The pathological characters of the hydatid cyst do not differ from those of a simple cyst. The adjacent parenchyma undergoes sclerosis on account of compression. If the hydatid cyst becomes infected, we have then the symptoms of a cystic strumitis. Clinically, the diagnosis of hydatid cyst is seldom made, as the only symptom pathognomonic of its presence, namely, the "hydatid fremitus," has never been perceived.

Treatment, of course, must be surgical.

## CONGESTIONS OF THE THYROID.

Possibly more than any other organ the thyroid is exposed to congestions of various origin, physiological or pathological. These congestions have a great clinical importance.

Physiological congestions are observed most frequently in women and especially during their genital life. Premenstrual congestion of the thyroid is among the most frequent premonitory symptoms of the first menstruation. Mothers often worry over this "physiological goiter." Not all have the wisdom of the one mentioned by Goethe, who said to

her daughter: "Do not worry, my child, Venus has touched thee with her enchanted hand."

Of course, in such conditions congestion is accompanied with true glandular hypertrophy. When once the menstruation is well established, congestion of the thyroid may subside more or less entirely. In many cases, however, it reappears each month with the menstrual period, and in *dysmenorrhœic* patients it may, indeed, be very marked, as if the thyroid were trying to exert a vicarious function.

That congestion in the thyroid takes place during the first sexual relations is a fact known since antiquity. It was a popular custom among the old Roman matrons to measure the circumference of the neck before and after marriage, and, as Berard says, "More than one Roman husband measured the virginity of his wife by the length of the thread wound around her neck."

Later on, during pregnancies and especially during delivery, the thyroid is again the site of congestion. This increase in volume is partly due, of course, to hypertrophy of the glandular elements, but active and passive congestions play a very important part in it also. After delivery, hypertrophy and congestion retrocede gradually, but, as a rule, the volume of the thyroid does not go back to its normal size.

At the menopause there is again occasion for congestions of the thyroid; they are the last "flaring up" of the genital process, which is going to be set at rest forever. Too often, however, these congestions of the menopause are of bad augury, as they are the premonitory symptoms of a malignant or of a thyrotoxic goiter.

In young boys these same transitory congestions may be seen at the time of puberty.

In conclusion, we may say that in human beings, the periods of life in which thyroid congestions most frequently occur are puberty, menstruation, pregnancy and menopause. During these periods metabolism is increased, and it is almost certain that this exaggeration of metabolism is due to increased thyroid activity.

The degree of change in the thyroid during puberty, menstruation and pregnancy, is normally slight, amounting to no more than the enlargement incident to the increased blood supply. Occasionally, hypertrophy of the epithelium occurs, and the iodine-content is usually diminished.

In rut and pregnancy of the lower animals, the thyroid changes are too slight to be easily detected, though many authors have reported mild degrees of thyroid hypertrophy in both these conditions. Marine has given considerable attention to the study of this feature but has never been able to detect any change in the size of the thyroid and in its histological appearance, nor was he able to find that the changes in the iodine-content were greater than the range of changes found normally



in either sex unassociated with sexual activity. An increase in metabolism occurs also in animals during rut and pregnancy, and therefore some increase in thyroid activity is probable, but it is too slight to be recognized by morphological or chemical changes in the thyroid, as can often be done in man.

Congestion following *physical effort* is a well-known fact, and is of frequent occurrence. Already, Lalouette and Maignien were aware of that fact. They demonstrated experimentally that in dogs, after a prolonged and fatiguing run, the thyroid became a third larger. This increase in size was due to venous congestion. These congestions due to physical effort are seen in all walks of life—singers, officers, workmen lifting heavy weights are especially liable.

Congestions in congenital goiter will be taken up in the chapter reserved for that subject.

**Pathological Anatomy.**—Very little was known of the congestive lesions in man until De Quervain, Berard, Ball and others approached this question experimentally. What strikes one's attention at first, is a marked dilatation of the bloodvessels of the capsule; they are abnormally distended and filled with black blood. On the cut surface the alveoli and capsular vessels are dilated and bulge out. Microscopically, besides the intense vascularization and the interstitial hemorrhages, what impresses one is the fact that the alveoli contain no colloid or very little, while the intra- and perilobular lymphatics contain a great quantity of it. At the same time a more or less intense desquamation of the epithelium is present.

**Symptoms.**—As a rule the only symptom seen in congestion of the thyroid is a swelling of the gland. Palpation shows an enlarged gland, rather firm, and slightly painful to pressure. It is only when a goiter of quite large size present that the congestions of the thyroid are liable to cause dyspneic symptoms.

The prognosis of thyroid congestions is usually extremely benign. After a few days or weeks the congestive symptoms retrocede and the gland is restored to normal. In the newborn the prognosis is not always so simple, as we shall see in the chapter on Congenital Goiter.

**Treatment.**—In the great majority of cases expectation is the only reasonable treatment. If during pregnancy the dyspneic symptoms become so marked as to endanger the life of the patient, thyroidectomy must be resorted to.

## TRAUMATIC LESIONS OF THE THYROID.

On account of its natural vertical as well as lateral mobility, and on account of the protection afforded to it by the muscles of the

cervical region, the thyroid gland is seldom involved in traumatism of the cervical region; however, injuries of that gland may occur and may be of such importance as to endanger the life of the patient and to call for immediate surgical help.

**Contusions.**—When a goiter more or less large in size is present, the traumatism does not need to be a great one in order to determine intraparenchymatous or intracystic hemorrhages. When this occurs, the increase in volume is sudden and may cause marked dyspnea. But when the thyroid is normal, the traumatism must be a severe one to determine lesions in the thyroid. This occurs mostly in strangulation, hanging, and other severe accidents bearing directly upon the thyroid. The consequences of such injuries to the gland are multiple; the most important are intra- and periglandular ecchymoses and hemorrhages.

The concomitant disturbances in respiration, phonation, and deglutition are nearly always due to fractures of the laryngotracheal cartilages. Thyroiditis may be the consequence of such contusions; even development of myxedema has been reported by Guerlain-Dudon as the result of a direct traumatism of the thyroid by the wheel of a wagon. Most likely in that case the gland underwent connective-tissue degeneration.

**Wounds.**—At the time when thyroid surgery was not so far advanced, *modifying* as well as *aspirating* punctures were the fashion. Sometimes they gave rise to very troublesome accidents. Aspirating punctures of an abscess or cyst often determined hemorrhages *a vacuo*; injections of modifying substances, as tincture of iodine for instance, were always most dangerous, and quite a number of sudden deaths have been reported after the use of such punctures. Today these therapeutic measures have been almost entirely discarded.

Wounds caused by *sharp instruments* are more serious. They occur, as a rule, in attempts to commit suicide, and are mostly situated in the upper portion of the lobe near the vascular pedicle, thus causing profuse hemorrhage. Such wounds, of course, are accompanied by injuries of the superficial veins, of the vessels of the capsule, and in some instances of the carotid sheath; even the laryngotracheal canal may have been opened. In all these traumatisms the hemorrhage is profuse, and death occurs if surgical help is not brought in time.

Before the antiseptic period, wounds inflicted with *firearms*, because of hemorrhage and suppuration, were more dangerous than they are today. This, however, was not always the case. At the battle of Cerisoles, commanded by the Duke d'Enghien, under François I, the young Swiss, Philip von Hohendax, who despite his youth had quite a large goiter, was struck in the neck with a large pick. The goiter, fortunately, was a large cyst, so that the accident proved a fortunate one, as it cured the patient of his goiter. Wounds by our modern rifles with

their small, thin bullets have proved more than once to be benign unless such injuries are accompanied by severe injury of other organs. On account of its speed and small size the bullet goes easily through the thyroid, making only a very small hole, and unless a vessel of importance is struck at the same time, the hemorrhage is not of great consequence, and is stopped automatically by the glandular débris formed by the passage of the bullet. Infections of such wounds are very uncommon. During the war between Japan and Russia and the late great war many of such cases were observed, but frequently no ill effects followed.

**Treatment.**—If surgical interference is thought necessary, the first indication is to widen the wound by a large incision, in order to be able to get a better view of the deep structures.

The second, to put hemostats on all the bleeding vessels and ligate them.

The third, to clean out thoroughly the surgical field if it is necessary.

The fourth, to sew up the injured gland either by continuous or interrupted sutures.

The fifth, only in very rare instances, when a lobe has been smashed into pieces, the resection of that lobe is to be given serious consideration.

The sixth, to leave a small drain for twenty-four to forty-eight hours or longer if necessary.

The seventh, to sew up the skin.

## CHAPTER VI.

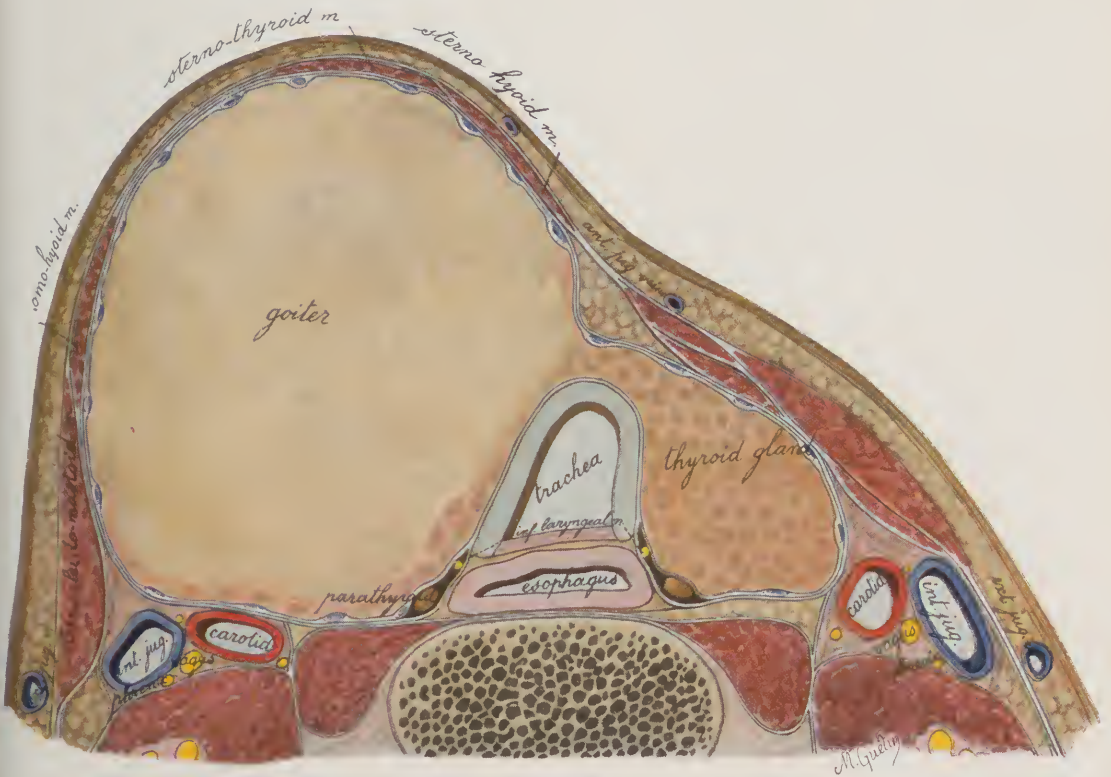
### ANATOMICO-PATHOLOGICAL RELATIONS OF GOITER TO THE SURROUNDING STRUCTURES.

STRUCTURES with which a goiter may come in contact are:

1. Sternocleidomastoid, sternohyoid, sternothyroid, and omohyoid muscles with their cervical fasciæ.
2. Larynx and trachea.
3. Pharynx and esophagus.
4. Bloodvessels, common carotid, superior and inferior thyroid arteries, internal jugular vein; in intrathoracic goiter both innominate, the arch of the aorta and the base of the heart may come in contact with the tumor.
5. Nerves: vagus with its superior and inferior laryngeal branches; sympathetic.
6. Sternum, clavicles and superior opening of the thorax.
7. While extending upward a goiter may come in contact with the hyoid bone, the digastric, hyoglossus and mylohyoid muscles, the submaxillary gland, and the hypoglossal nerve.
8. While developing laterally, a goiter may fill the posterior triangle of the neck, compress the spinal accessory nerve and go as far as the anterior border of the trapezius muscle.
9. Owing to the fact that the thyroid gland lies on a hard surface, formed by the transverse processes of the cervical vertebræ, covered by the deep muscles of the neck, a growing goiter must naturally develop forward, laterally, and downward; its upward extension is less frequent, and is found mostly in certain large parenchymatous goiters, and in those developed in the upper poles or in the pyramidal process.
10. The relations of a goiter to the surrounding structures will differ notably if we have to deal with a *diffuse parenchymatous* goiter or a *nodular* one.
11. A *diffuse parenchymatous goiter*, unless of unusual dimensions, occupies the position of the normal gland, and consequently has no material influence on the surrounding structures. On the whole, it retains the shape of the normal gland. Only in very voluminous goiters do we see the upper poles extend upward as far, sometimes, as the angle of the jaw and then come in contact with the thyroid cartilage, the hyoid bone, the mylohyoid and digastric muscles, and the hypoglossal



PLATE VI



Cross-section of the Neck Showing the Relation of a Goiter to the Surrounding Structures.



nerves. In its downward growth the goiter grows alongside and in front of the trachea and esophagus, in front of the carotid sheath and of the vagus and sympathetic nerves. Anteriorly, the two hyperplastic lobes and isthmus cover a more or less great portion of the trachea, of the cricoid and thyroid cartilages. The processus pyramidalis participates, as a rule, only to a moderate degree in the hyperplasia. Laterally and in front the goiter is covered by the muscles of the cervical region.

If hyperplasia is more or less evenly distributed over the whole of the thyroid, there is practically no displacement of the trachea and esophagus; displacement of the latter organs takes place only when one lobe of the gland is larger than the other one. However, displacement or compression of the windpipe is seldom severe with diffuse parenchymatous goiters. In that type of goiter we do not find the intense dyspnea and the same intensity of choking spells that we encounter in nodular goiter. If, however, the hyperplastic goiter grows around the trachea and esophagus so as to form a "circular goiter," then dyspnea and dysphagia may be quite marked.

Because the diffuse parenchymatous goiter, especially when it has reached large dimensions, compresses the large vascular trunks on both sides, and because, too, such goiters more than any others, except the thyrotoxic, are subjected to congestions, impairment of the venous circulation of the neck is not uncommonly seen. It does not, however, reach the same degree of intensity as in intrathoracic goiters.

Nerves are very rarely injured by the diffuse parenchymatous goiter; the inferior laryngeal nerve, however, may show some symptoms of compression.

Not infrequently does the diffuse parenchymatous goiter extend downward behind the sternum. When it does, it is only in a moderate degree, and especially in cases where the thyroid is situated abnormally low (thyroptosis of Kocher).

Entirely different are the relations of the *nodular goiter* to the surrounding structures. Of course here, again, such relations are determined by the size of the goiter. (Plate VI.)

**Relation of Goiter to Skin and Muscles.** (Plate VI).—In certain forms of goiter, especially in *pendulous goiter*, the skin may become so distended and elongated as to form a real cutaneous pedicle.

At first, during the slow but progressive growth of the goiter, the cervical muscles covering the goiter undergo a certain amount of hypertrophy, thus forming a powerful muscular belt whose spasmodic contraction during choking spells can but increase their intensity. This is proved by the fact that the transverse section of this muscular belt relieves dyspnea very materially. Later, however, when the nodular

goiter has reached voluminous dimensions, on account of prolonged pressure and displacement, the muscles finally undergo atrophy and degeneration; the muscular fibers become thin, pale, friable, dissociated, sometimes hardly recognizable. The sternocleidomastoid muscles, too, participate in this atrophy, although in a lesser degree.

**Relation of Goiter to the Larynx and Trachea.** (Plate VI). —Already in 1817, Aepli, then Soemmering in 1820, and others called attention to the various forms of deformation of the trachea most frequently seen in connection with goiter. In 1861, Demme gave a masterful description of the pathological trachea in goiter and called attention especially to the “sabre-sheathed” trachea (Fig. 26). These deformations were thought to be of solely mechanical order. In 1878, however, Rose, although admitting that the etiology of tracheal deformations was partly mechanical, insisted that a great number of sudden deaths seen in such conditions was due to the sudden collapse of the walls of the windpipe on account of their *degeneration* and *atrophy*. The microscope showed that not only congestive lesions of the mucous membrane were present, but that also a marked fatty degeneration of the cartilaginous rings of the trachea and of the elastic and muscular fibers of the posterior membrane had occurred. Demme, Eppinger, Berard and others have more or less confirmed these findings. Indeed, it seems logical to admit that an organ which is constantly undergoing pressure is bound to undergo atrophy and degeneration in the course of time. At any rate, one who has seen goiters knows that the “ribbon-shaped” trachea is not rare, and that mechanical and secondary alterations intervene to form such a trachea.

Tracheal deformations in nodular goiters are found in about 50 per cent. of the cases. This has been confirmed by O. Wild with tracheoscopy, and by Pfeiffer with radiography.

The effects of pressure on the windpipe are manifold:

1. If the nodular goiter develops in one lobe, the other one being more or less normal, the trachea assumes a curved direction with the convexity toward the sound side (Fig. 25). At the same time the trachea and larynx rotate around their long anterior axis because the latter one is held more or less firmly by the thyroid suspensory ligament and the hyoid bone, whereas the posterior border is free from such attachment; it rotates along the anterior border acting as a hinge and in the opposite direction to the pressure.

2. If a nodular goiter is developed in each lobe, and if these two goiters are more or less on the same level, the trachea may be so compressed on each of its sides that the walls of the trachea may come in contact, one with the other, and form what we call the *sabre-sheathed* trachea (Fig. 26). This form of deformation of the trachea, although possibly



less frequent than the former, is infinitely more dangerous, and is the one which may prove fatal. This is easily explained. Although as the result of pressure the walls of the trachea may have undergone considerable atrophy, as long as the trachea remains in intimate connection with the goiter, the latter playing the role of a splint, there is no chance for the tracheal walls to be sucked in during inspiration. But let us remove the goiter. Then, atrophied, degenerated, and having lost their normal resistance and elasticity, the walls of the trachea are unable to withstand successfully the changes of air-pressure in the bronchial tube;

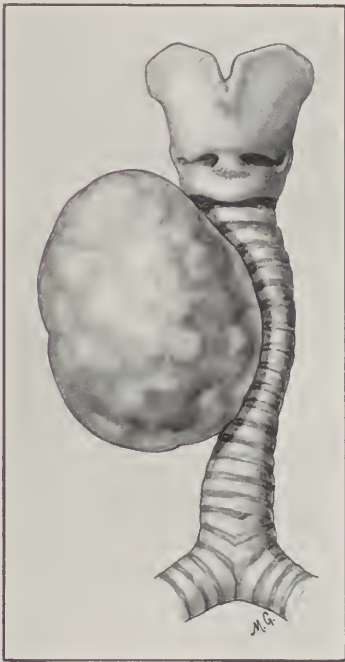


FIG. 25.—Unilateral compression of the trachea by a nodular goiter.

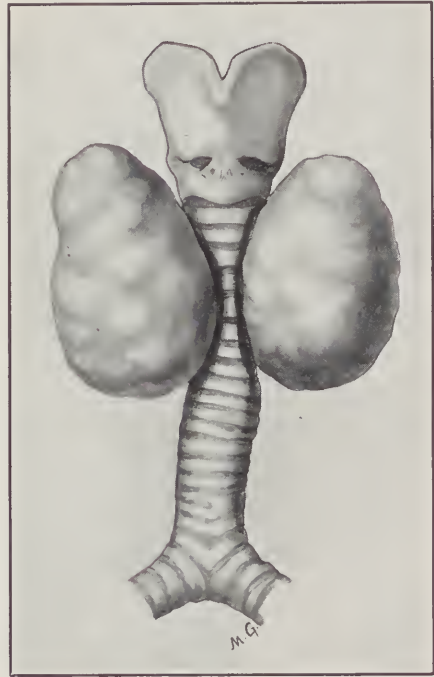


FIG. 26.—Bilateral compression of the trachea taking place at the same level. Sabre-sheathed trachea.

they flap in and out, expand during expiration and collapse during inspiration: hence suffocation. The more laborious the inspiration is, the tighter is the suction. Every surgeon has probably more than once experienced such a tracheal collapse during operation. At any rate, everyone who does thyroid surgery should be acquainted with such an eventuality, and should know how to guard his patient against it.

3. If two nodular goiters develop in the lobes, but at different levels, then the trachea assumes an S-shape analogous to the scoliosis of the spinal column (Fig. 27).

4. If a goiter develops in the isthmus, its size does not need to be very large to produce symptoms of pressure. As the isthmus is firmly attached to the cricoid cartilage by the thyroid suspensory ligament a goiter developed in the isthmus will naturally not be able to wander far, even if it attains a large volume; it is kept in front of the wind-pipe, where compression takes place anteroposteriorly, which fact is soon

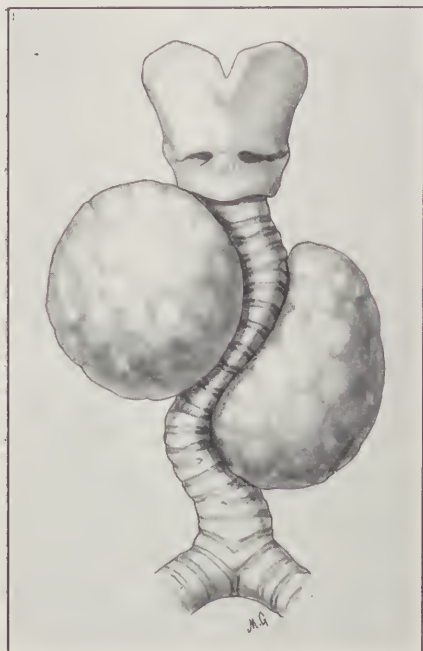


FIG. 27.—Bilateral compression of the trachea taking place at two different levels, thus forming the S-shaped trachea.

betrayed by marked dyspneic symptoms (Fig. 28). In such conditions the large diameter of the tracheal lumen is frontal, whereas in the sabre-sheathed trachea it is sagittal. Such a goiter is called *struma mediana* or *median goiter*. In its further development the median

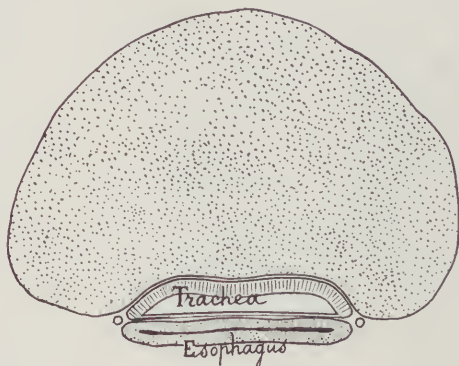


FIG. 28.—Pressure on the trachea and esophagus taking place anteroposteriorly.

goiter may gradually sink downward and become intrathoracic. This goiter rarely develops in the isthmus alone; as a rule it develops at the junction of the lobes with the isthmus.

5. A goiter developed in the *processus pyramidalis* is a rare feature. It is situated in the middle line or a little outside of it, high up in front of the larynx, and is quite superficial. Let us call this form of goiter *pyramidal goiter* (Fig. 29).

6. In certain cases, especially in newborn, each lobe of the thyroid may extend behind the trachea and esophagus to such an extent as to come into contact one with another; the trachea and esophagus are then surrounded with a ring of glandular tissue. This is the *circular goiter* (Fig. 50). We shall study it in a chapter by itself.

Besides the trachea, the larynx may, too, be compressed and displaced by a large goiter. Such modifications of positions of the larynx

and changes of consistency of its cartilages are apt to cause phonetic disturbances, due only to a rupture of the anatomical, static and muscular equilibrium; the vocal cords may be normal but the points of insertion are slightly displaced; hence a slightly disturbed synergical action of both cords.

As can be easily foreseen, all these pathological modifications of the laryngotracheal tube give rise to congestion of its mucous membrane, and as these irritations are eminently chronic, the mucous membrane becomes edematous, thickened and congested. The clinical importance of these lesions cannot be ignored. Take, for instance, cases in which tracheo-



FIG. 29.—Goiter developed in the pyramidal process.

stenosis is so developed that the patient has barely enough lumen left for respiration. Suppose now that for some reason an active or passive congestion takes place in the tracheal canal, the mucous membrane at the level of the tracheal stricture becomes so edematous that the respiratory lumen becomes insufficient, suffocation follows, and death may ensue.

**Relation of Goiter to the Pharynx and Esophagus.** (Plate VI).—In ordinary goiters the pharynx and esophagus are seldom involved. Deglutition is interfered with only when the goiter has become adherent to the walls of the esophagus either because of a strumitis or because of a

fibrous or malignant goiter. There too, as in the trachea, a long, continuous pressure on the esophageal walls may cause such an atrophy as to perforate them, and yet such goiters may *not* be malignant at all; but, of course, this is rare.

**Relation of Nodular Goiter to Bloodvessels.** (Plate VI).—In large goiters the common carotid is displaced posteriorly and laterally; it may even be found in the posterior triangle of the neck. I have seen it more than once not far from the anterior border of the trapezius. The carotid is then found enlarged, has sometimes a tortuous course, is subcutaneous, and is felt as a tense, expansive cord.

When the common carotid has contracted intimate relations with the capsule of the gland, on account of strumitis or for any other reason, this posterolateral displacement of the vascular trunk is easily understood; yet such displacements happen in goiters in which no inflammation whatever is found. It then finds its explanation in the anatomical relation between the thyroid gland, the common carotid and the superior thyroid artery. In undergoing upward enlargement the goiter seems to grow in the angle formed by the carotid and the superior thyroid artery. As the latter is firmly fixed by its two terminal branches to the thyroid it holds tightly the common carotid to the posterolateral surface of the goiter in the same manner as if someone should carry somebody on the back or over the shoulders by holding him tightly by the arm. The more the goiter grows, the tighter becomes the relations between the goiter and carotid, consequently the more the carotid will be displaced laterally and posteriorly. At the same time it becomes elongated; in voluminous goiters this elongation of the common carotid may be sometimes quite marked. Wölfler saw a case in which the carotid formed around the goiter a segment of a circle whose radius was 6 cm.

The outward displacement of the carotid has a very important diagnostic value, because it is caused by goiter and by nothing else. In tuberculosis or malignant tumors of the cervical lymph nodes the common carotid, instead of being displaced outward, lies in the center of the tumor. Again, anatomy will give us the reason for it: normally, the lymph nodes are found all around the carotid sheath, consequently in tumors of the cervical lymph nodes the common carotid must naturally lie in the middle of the tumor.

The *superior thyroid artery* loses its normal anatomical relations only in large-sized goiters. In that case, very much increased in size, this artery follows a sinuous course, separated, to a more or less extent, from its normal anatomical neighbors, namely, the inferior constrictor of the pharynx and the superior laryngeal nerve. The point of election for its ligation is the superior pole.



Lying directly on the prevertebral fascia the *inferior thyroid artery* may be easily compressed and displaced by a growing goiter. In partly intrathoracic goiters this artery is covered entirely by the tumor and is consequently difficult of access for ligation. As a rule, the safest place to ligate the inferior thyroid artery is *inside* the carotid sheath, between this sheath and the thyroid gland. The ligation of the artery near its point of entrance into the thyroid is dangerous, inasmuch as the parathyroids and the inferior laryngeal nerve might easily be injured.

In large goiters the veins of the neck are distended because the return flow of blood is impaired by compression on the large venous trunks or because of some pathological disturbances in the right heart; as a result of this, intense venous congestion is seen in all the cervical region; the anterior jugular, the superior thyroid, the imæ veins and all the capsular veins may be so distended that the gland seems to be the site of an angioma. These imæ veins must be known to the surgeon, as they are the ones most apt to allow air embolism. In all these conditions the distended veins are friable and thin. They have lost their elasticity: hence, the frequent venous parenchymatous hemorrhages which may sometimes become alarming.

**Relation of Goiter to Nerves.** (Plate VI).—The nerves which are mostly involved in voluminous goiters are the *vagus* and the *sympathetic*. Compression on the vagus trunk itself does not give rise to any special symptoms. Its branch, the *superior laryngeal nerve*, even when materially compressed and displaced, does not cause appreciable functional disturbances. On the contrary a slight injury to the *inferior laryngeal nerve*, which is another branch of the vagus, has the most unpleasant consequence, as it may mean for the patient total loss of voice. After thyroidectomy this symptom may be the only living witness of the awkwardness or ignorance of the surgeon. As a rule this nerve is compressed in the inner and posterior angle of the tumor, and as a result of this, paralysis of the corresponding vocal cord may follow. The same thing may happen if the goiter has been the site of a hemorrhage or strumitis, because the nerve becomes adherent to the capsule: hence functional disturbances.

That the *sympathetic nerve* may be involved in large growing goiters is made clear by its anatomical relations. It may become compressed on the prevertebral surface or it may be traumatized with each pulsation of the inferior thyroid which comes in contact with it and with the middle cervical ganglion. Traumatism of the cardiac branches of the sympathetic may account, too, for some forms of tachycardia.

The *hypoglossal*, *spinal* and *phrenic nerves*, the *cervical* and *brachial plexuses* may be involved, too, by the large growth of the goiter.

## CHAPTER VII.

### CLINICAL SYMPTOMS AND DIAGNOSIS.

#### CLINICAL SYMPTOMS OF GOITER.

A GREAT many goiters, at least for a considerable period of time, have no history. They do not betray their presence by any mechanical or functional symptoms. In their early stage, when symmetrically placed, they give to the neck a soft roundness called "swan-neck," and are considered in many countries one of the attributes of feminine beauty. Many of the great artists of the past centuries shared the same views, as one can easily convince himself, if he cares to, by visiting certain museums.

Although sometimes a slight apathy, thickening of the teguments, constipation, chilliness, etc., indicate a slight degree of thyroid insufficiency, while in other cases a slight tachycardia, nervousness, impatience in disposition, abruptness of movements and brilliancy of the eyes betray the first symptoms of hyperthyroidism, these patients are absolutely unaware of their condition and would sneer at one who would tell them that they are sick.

At the time of *puberty* especially, and later on with each menstrual period, young girls often complain of constriction of the neck, of choking sensation, of coughing spells; during sleep they are frightened with distracting nightmares; in daytime they easily get tired, complain of palpitation, nervousness, tremor, etc. All these symptoms, partly mechanical, partly thyrotoxic, are due to a slight parenchymatous goiter which so often accompanies puberty. In the great majority of cases they subside; in others, however, they progress and develop into a permanent parenchymatous or nodular goiter, be it toxic or not.

A goiter may cause *mechanical* and *functional* symptoms.

**Mechanical Symptoms.**—The *mechanical* disturbances can be easily foretold after our study of the relations of a goiter with the neighboring tissues. We must remember that the symptoms are not always in direct proportion to the size of the goiter; a small median or retrosternal goiter will cause far more serious symptoms than a voluminous goiter hanging in front of the thorax.

**Dyspnea.**—One of the main symptoms which causes the patient to seek medical attention is *dyspnea*. It may be produced:

1. By direct pressure on the trachea.

2. By an injury of the inferior laryngeal nerve, causing paralytic conditions of the vocal cords.

3. By venous congestion of the cervical region and the upper part of the mediastinal space following pressure upon the nervous trunks.

Dyspnea is a slow-developing symptom. For a long time the patient is not aware that he is getting out of breath easily, that while talking he must stop frequently to draw a deep breath of air. In time, however, he becomes conscious that he is no longer able to climb stairs or to do any physical exercise without losing his breath. Gradually respiration becomes more and more laborious, and when finally, on account of pressure, the lumen of the trachea has become greatly narrowed a long, loud, whistling inspiration is heard: that is the *tracheal stridor*. Stridor is mostly *inspiratory*, but may be *expiratory* also. Dyspnea may be constant or *paroxystic*. When the trachea is greatly constricted, a slight physical exertion, a simple movement of the head, or a catarrhal congestion of the laryngotracheal tube, or any sudden pressure from without, is sufficient to cause attacks of asphyxia. When compression, even of moderate degree, is of years' standing, a permanent congestion of the entire respiratory apparatus takes place, and, as a consequence of this catarrhal conditions and of the tracheal stenosis, emphysema and bronchiectasis develop. Furthermore, when the blood circulation in the lower portion of the lungs becomes sluggish there is a marked tendency to congestion, bronchitis, bronchopneumonia, etc. As a result of pressure upon the large cervical and intrathoracic venous trunks, stasis takes place in all the upper venous system, hence vertigo, headache, congestion of the face, nose-bleeding, somnolence, etc. Like stridor, dyspnea is more frequently *inspiratory* than *expiratory*.

**Dysphagia.**—Difficulty in swallowing is especially noticeable in the retrovisceral and intrathoracic goiters. The patient seldom complains of pain in swallowing; he may, however, have some difficulty in swallowing solid food, yet in uncomplicated goiters an absolute impossibility of doing so is not known.

**Vocal Disturbances.**—The *voice* in large goiters is characteristic; it has a thick, guttural, impure tone, as if the vibrations were muffled. This is due to the congestion of the mucous membrane of the laryngotracheal tube and to the slight displacement of the points of insertion of the vocal cords; on that account they cannot ring true. If to that we add a muscular insufficiency, and possibly to some involvement of the inferior laryngeal nerves we will understand why during the speech of patients with large goiters, changes in the voice appear so brusquely, why certain sounds are not uttered, why "slips of the voice" occur, the whole thing making, as Berard says, a motley mixture of *couacs* and *silences* which are very peculiar and characteristic. The voice assumes a bitonal character. This is the *bitonal voice*.

**Symptoms Due to Injury of the Inferior Laryngeal Nerve.**—Bilateral paralysis of both inferior laryngeal nerves is found only in malignant goiters. In the benign form of goiters, irritation of the inferior laryngeal nerve is nearly always *unilateral*; it then determines tonic contractions of the vocal cords of the same side, which give to the voice a *bitonal* character. It may cause, too, coughing spells and spasm of the glottis, which may be so marked as to cause the most alarming symptoms of suffocation. Cough of *recurrent nerve origin* differs clinically from the one resulting from compression on the bronchotracheal tube. We can say with Varay that they constitute two distinct types:

1. The cough of *recurrent type*.
2. The cough of *compression type*.

The “recurrent cough” is dry, loud and not accompanied with expectoration. It comes on mostly by spells. The “compression cough” is sonorous, deep, cavernous, with a grave, metallic sound, resembling the cough of a dog choking with a bone in his throat; it is really a “barking cough.” Brought on by slight physical effort, it does not seem to annoy the patient as much as the noise would indicate.

When compression on the inferior laryngeal nerve is only slight, it manifests itself by a metallic sound of the voice, due to a paretic condition of the vocal cord involved. As long as the inferior laryngeal nerve has not been destroyed the patient remains exposed to sudden and unexpected spasms of the glottis because the constrictor muscles of the glottis resist longer than the dilatators; the latter are put out of function a long time before the former. On the other hand, when the process of irritation or paralysis of the recurrent nerve retrocedes, as Rosenbach and others have shown, the dilatator muscles are the last to recuperate their function.

Paralysis of the recurrent nerve, as a rule, takes place gradually; it may, however, be sudden, as in cases in which a brusque compression due to an intracystic hemorrhage occurs. When paralysis of the nerve is complete, then there is a paralysis of the corresponding side of the glottis; the vocal cord of the paralyzed side takes an “intermediary” position, and as the vocal cord of the sound side does not go beyond the middle line, phonation is, of course, impossible; hence complete *aphonia*. Later, however, the sound vocal cord increases its radius of excursion, swings over the middle line in order to come into contact with the paralyzed cord: *aphonia* then disappears. The patient may even seem to have regained his normal voice; his singing voice, however, never returns.

In goiter, injuries of the inferior laryngeal nerve are relatively frequent. They are mostly characterized by symptoms of slight importance, and according to statistics, the frequency of such lesions varies in



from 7 to 35 per cent of the cases. Lesions of the inferior laryngeal nerve predominate on the left side as a rule. Avellis found that out of 150 recurrent laryngeal paralyses 46 were on the right side, 92 on the left, and 12 were bilateral. B. Mathews out of 289 partial or complete paralyses found 93 on the right side, 162 on the left, and 17 bilateral. Predominance of paralysis on the left side may be accounted for by the fact that the left inferior laryngeal has a longer course, and is more exposed to pressure not only in the mediastinal space but also in the cervical region, as it is more superficial than the right. Although the frequency of pressure symptoms on the recurrent nerves is in direct proportion to the size of the goiter, Mathews found some exceptions: small goiters, hardly large enough to be recognized, may produce symptoms of paralysis, whereas large ones may not cause any. Men are about three times as liable as women to have paralysis of the inferior laryngeal nerves.

The trunk of the *vagus nerve* itself is seldom involved except in strumitis and cancers. In rare instances the slowness of the pulse and respiration have been interpreted by some authors as due to mechanical traumatism of the vagus nerves.

So far as the *sympathetic nerve* is concerned it is not always easy to recognize clinically the symptoms which belong to mechanical compression of the sympathetic nerve itself; if, however, the sympathetic symptoms are localized on one side of the face only then the diagnosis of compression on the sympathetic side can be made with certainty. The symptoms of *excitation* of the sympathetic are a unilateral exophthalmos with dilated and sluggish pupil, enlargement of the palpebral fissure, and redness of one cheek more marked than the other. The symptoms of paralysis are ptosis of the eyelid, thus producing a smaller palpebral fissure, myosis, on account of paralysis of the dilatator muscles of the pupils, redness of the ear, and abundant perspiration on the paralyzed side.

In extremely rare cases the *spinal nerve* is involved; a *torticollis*, or wry-neck, due to spasmodic contraction of the trapezius and sternocleidomastoid muscles, is then the consequence of it. The lesions of the *hypoglossal nerve* occur only in goiters developed from the thyroglossal duct. In such conditions a paresis and an atrophy of the corresponding side of the tongue have been observed. Symptoms of compression of the superficial cervical plexus are found sometimes in voluminous goiters and are characterized by irradiating pains toward the auriculotemporal and occipital regions. When pressure takes place on the deep cervical plexus, *pectoral neuralgia* and painful formications along the arm and hand have been reported. The *phrenic nerve*, especially in retrosternal goiters, may be caught and compressed in front of the scaleni muscles;

this is rare, however. In such conditions hemispasm of the diaphragm will be present, followed later by paresis or paralysis of that muscle.

**Functional Symptoms.**—Functional symptoms can be divided into two large classes: the symptoms of *hypothyroidism* and those of *hyperthyroidism*. They will be studied in separate chapters.

The *goiter-heart* will be studied in a chapter by itself.

### DIAGNOSIS OF GOITER.

In the great majority of cases, diagnosis of goiter presents no difficulty. First of all the history of the patient puts us at once on the right scent by telling us if the patient comes from a country where goiter is endemic or not, if other members of his family are affected with it or not, or if he complains of mechanical or thyrotoxic symptoms. When dealing with a tumor of the neck, the two important things which we have to decide are:

1. Is the tumor in the thyroid?
2. What is its nature?

1. **Is the Tumor Developed in the Thyroid.**—*Inspection* shows the form, volume and position of the goiter. It shows the condition of the skin of the neck, whether there is any congestion of the face, any collateral circulation on the neck or thorax, any dyspnea, any symptoms of irritation or paralysis of the sympathetic, or whether any thyrotoxic symptoms as tremor, exophthalmos, etc., are present.

There is one symptom which is pathognomonic for tumors of the thyroid: that is, the up-and-down movements which the tumor follows during deglutition. As the thyroid is intimately connected with the cricoid cartilage through its suspensory ligament, the tumor is bound to follow the larynx in its up-and-down movements. This symptom seldom fails. Only when the goiter is extremely large or when it has a long, loose pedicle, these up-and-down movements may be doubtful. But even then a little trick may solve the problem. By placing the patient's head in hyperextension and asking him to swallow, it would be very surprising indeed if these up-and-down movements are not obtained; exceptionally, however, when the tumor has developed at the cost of an accessory thyroid gland, or when a malignant tumor or a strumitis has walled in all the organs of the cervical region, then these up-and-down movements will not be detected.

*Palpation* must be done methodically. We must begin by ascertaining if possible the exact position of the thyroid and cricoid cartilages and the trachea to see if they are displaced on one side or the other. When that is done the two lobes, isthmus and pyramidal

process, are carefully investigated separately, their consistency, their surface, their mobility and their relation to surrounding structures being carefully noted.

We shall find that in the greatest number of cases, the goiter is more mobile transversely than vertically, that during deglutition the tumor slips out of the palpating hand to follow the up-and-down movements of the larynx. We must then endeavor to outline the inferior limits of the tumor. The best way to do so is to palpate with the thumbs, the palms of the hands and fingers reposing on the shoulders. The patient is requested to flex his head forward and laterally in order to relax the muscles of the side subjected to examination. This facilitates, too, the palpation of the retrosternal region. With some care and skill it will then be possible to fish out of the thorax quite a number of partially intrathoracic goiters which were never suspected before. When a goiter is a multinodular one, pressure on each nodule separately may reveal the one which is causing most of the pressure symptoms.

Palpation will, furthermore, show that the common carotid is possibly displaced laterally and posteriorly; in that case it is felt pulsating subcutaneously. The condition of the superior thyroid arteries is ascertained. If a goiter shows pulsation, we must determine if this pulsation is only transmitted or if it is really an expansive one.

*Percussion* over the thorax is intended to show if there is a dullness caused either by an intrathoracic goiter, a thymus hyperplasia, or any other mediastinal tumor. It conveys, too, some information as to the condition of the lungs and the size of the heart.

*Auscultation* will tell us if a systolic murmur is present over the gland, especially at its upper poles. It will tell us, too, if there is compression upon the trachea by the tumor. In that case we shall hear, especially over the manubrium sterni, a rough inspiration followed by a prolonged, loud expiration, unmistakably accompanied with tubular breathing. I consider this finding as an excellent sign of compression. Finally, auscultation will inform us as to the true condition of heart and lungs, the knowledge of which is of the utmost importance when it comes to prognosis and treatment.

**Laryngoscopic Examination.**—Laryngoscopic examination shows the condition of the vocal cords. This examination should be made as a routine procedure before operation, if only as a protection to the surgeon in order to avoid being held responsible for an injury to the inferior laryngeal nerves which existed prior to the operation. Tracheoscopy is seldom indicated.

An x-ray, if deemed necessary, will then terminate the examination and corroborate or disprove many of the clinical findings. It will add, furthermore, precious information about the size of the intrathoracic

goiter, if there is any, about the displacement and compression of the windpipe, about the presence of thymus hyperplasia, etc.

**2. What is its Nature?**—When once we have decided that the tumor is of thyroid origin we must then decide what its nature is. In diffuse parenchymatous goiter the gland *in toto* is enlarged, of firm consistency, and finely granular. The gland has more or less kept its normal, general outlines unless the diffuse enlargement should affect one lobe more than the other. By closer examination it is not uncommon to find small nodules of harder consistency spread throughout the gland. In colloid goiters the gland has lost its regular form, and colloid degeneration is more marked in one lobe than in the other; hence the irregularity in the form of the thyroid. The surface is lobulated, nodular on account of the presence of colloid nodules of different sizes; consistency may be firm, but in cases in which the colloid nodules are large and of different volumes the consistency may vary considerably, being firm in places, hard in others, and soft in others. Fibrous goiter is characterized by its hard consistency, and differs from the calcareous goiter by its small size, though this is not always the case. Cystic goiter is not difficult to diagnose, especially when it has attained a certain size; its surface is smooth, the tumor is mobile, elastic or fluctuating. When fluctuation is present the diagnosis of cyst is almost certain. I say almost certain because a pseudofluctuation sometimes seen in some colloid nodules may lead one to believe that he has to deal with a cystic tumor when such is not the case.

Vascular goiter is of rare occurrence except in exophthalmic goiters. In that case the diagnosis is easily made. In genuine non-toxic vascular goiter the tumor is soft and can be reduced in size by compression. A marked vascular murmur is heard over the gland and especially at its poles. Thrill and expansive pulsation are present.

In a great majority of cases the differential diagnosis between goiter and any other condition is hardly necessary. When the tumor is median, a cyst developed from the thyroglossal duct might be confused with a median goiter. But, as a rule, this thyroglossal cyst lies in exactly the middle line and is found mostly between the hyoid bone and the thyroid cartilage, whereas a median goiter is situated below the cricoid.

Congenital cysts of the neck of thymic origin are located along the anterior border of the sternocleidomastoid; they are independent of the trachea and larynx and do not follow their up-and-down movements during deglutition. The same is true of tuberculous glands; their anatomical relations, their consistency, their pathological characters, and the history of the development of the disease differ entirely from those of goiter.



## GOITER-HEART.

That there exists a relation between goiter and the heart was, of course, observed long ago. Rose first thought that the goiter-heart in connection with stenosing goiters was due to pressure on the blood-vessels of the thorax. Kocher not only admitted this fact as an etiological factor, but added that impairment of the respiration was also a cause of goiter-heart, and called it *dyspneic goiter-heart*.

Schranz believed that goiter-heart was caused by venous stasis in the thorax, causing hyperemia of the heart muscle, and subsequently an excitation of the cardiac ganglia: hence, increased cardiac activity, then hypertrophy, dilatation and finally degeneration of the muscle. Wölfler took a similar view.

Kraus designated as goiter-heart the cardiovascular symptoms caused not by mechanical pressure but by the exaggerated function of the thyroid gland and its action on the cardiac apparatus. Kocher shared this same view and differentiated this goiter from the mechanical goiter-heart.

To Minnich we owe an excellent contribution on the question of goiter-heart of *pneumonic origin*.

There are two separate and distinct varieties of cardiac disturbances that may occur in connection with goiter, the *mechanical goiter-heart* and the *thyrotoxic goiter-heart*. Kocher distinguished a third form which is rare: this condition of the heart is caused by compression of the large vessels and nerves by a large goiter. This goiter is then called *cardiopathic goiter*.

**The Mechanical Goiter-heart.**—It is easy to understand that being given their anatomical relations with the thyroid gland the vagus and the sympathetic nerves may be mechanically traumatized by a large goiter. These lesions, however, are rare; when present they are mostly unilateral. Bilateral compression on the vagus and sympathetic by a simple goiter, to my knowledge, has never been observed. Far from me, however, be the idea that is not possible. It may occur in malignant goiters. Furthermore, there are a great many goiter-hearts in which traumatism of the vagosympathetic system cannot be rightfully incriminated on account of the small size, location, etc., of the goiters. If we stop to consider the close anatomical relations of the vagus and sympathetic, it is hard to admit that traumatism can affect one nerve and not the other. It seems to me that both must be injured at the same time. If that is the case, since the vagus is a *moderator* and the sympathetic an *accelerator* of the cardiac action, these two nerves should counterbalance their action. We know indeed that irritation of the sympathetic with the faradic current produces physiologically a slight acceleration of the cardiac

action, whereas the same irritation of the vagus produces a moderation. Surgical experience shows, on the other hand, that division of both vagi or both sympathetics has no effect, or very little, on the frequency of cardiac action.

Goiter-heart is really peculiar to goiter only. It is not found in the malignant degeneration of cervical lymph nodes, in Hodgkin's disease, etc., where certainly the chances for having an involvement of the sympathetic and vagus are greater. Why is it? We shall see later.

So the theory that considers pressure on the vagus and sympathetic nerves as the etiological factor of goiter-heart is, in my judgment at least, not altogether satisfactory.

The pressure on the bloodvessels of the thorax, as advanced by Rose, must be regarded as an important etiological factor of goiter-heart. It causes venous stasis in the thorax leading naturally to stasis in the right auricle and ventricle: then follows dilatation, and after a while degeneration of the heart muscle.

But this is not all. The impairment of respiration, as Kocher and Minnich have pointed out, also intervenes as a cause of goiter-heart. In order to understand how this occurs we must study the physiology of respiration and circulation.

Normally there is in the thorax a negative pressure. This negative pressure is always constant, and is never reduced to zero even in forced expiration. The consequence of it is that the extrathoracic pressure is higher than the intrathoracic one. For this reason the blood is aspirated toward the thorax; this fact is called the *thoracic suction*.

During diastole the heart increases actively the size of its chambers, and by so doing creates in them a vacuum which aspirates the blood of the tributary vessels. With Minnich let us call this *ventricular suction*.

Thoracic and ventricular suction are two of the main factors which, in the thorax, aspirate the blood toward the heart. Of course, other important factors come into play, but they are without importance so far as the explanation of goiter-heart is concerned.

During inspiration the thorax increases its capacity, hence the negative pressure increases and consequently the thoracic suction increases, too. During expiration the thorax contracts, the lungs expel the air contained in the alveoli; as a result the negative pressure is diminished, and, *ipso facto*, the thoracic suction. As a consequence of this fact there is normally during inspiration an increased quantity of blood aspirated toward the right auricle and ventricle. During expiration this quantity is diminished.

During these physiological phases the quantity of blood, and consequently the pressure in these chambers, would soon run above normal if there was not a compensatory process to prevent such excess. This

compensation is furnished by the capillaries of the lungs. During inspiration they follow the expansion of the lungs, increasing their capacity, so that the blood running toward the heart is partly side-tracked. By this process the pressure in the right heart is maintained normal. Minnich called this fact the *pulmonary compensation*.

The effects of respiration on the left heart are quite different and very much less marked, because of the size and of the thickness of its walls; however, during inspiration the pressure in the left auricle and ventricle diminishes in a moderate degree, and during expiration increases in the same proportion.

These few physiological explanations will enable us to understand what happens in cases of stenosis, due to goiter or any other obstacle to respiration.

In inspiratory dyspnea, when a patient takes a deep breath in order to get enough air, the thorax expands to the maximum, so that the negative pressure in the thorax is greatly increased. In such conditions the blood is aspirated toward the right heart with great speed, but unfortunately, on account of the goiter-stenosis, the lungs do not follow the expansion of the thorax. Consequently the capillary bloodvessels of the lungs do not dilate; in other words, pulmonary compensation does not take place; the blood is not side-tracked in proportion to the stream running to the right heart, hence the dilatation of the right heart. The consequence of this is that the pressure in the pulmonary artery diminishes, and as a result there is, too, a diminution of pressure in the pulmonary vein, in the left auricle and in the left ventricle. If the musculature of the right heart is still in good condition, it will compensate by overwork the rupture in the balance of pressure between the right and left heart, and we shall then have a hypertrophy of that section of the heart. If the musculature is degenerated we shall have failure of compensation and its results.

In expiratory dyspnea during the effort of expiration the negative pressure is considerably diminished. For this reason the blood is kept back in the tributary veins: the volume of blood coming to the right heart is considerably diminished, but with the following inspiration all this blood which has been kept back flows toward the right auricle and ventricle and would soon overwhelm this segment of the heart if the compensation of the lungs did not take place and did not sidetrack the surplus of blood. But suppose the expiratory dyspnea is of long standing, having caused emphysema, bronchiectasy, and chronic catarrh of the respiratory apparatus, then in that case the capillaries of the lungs undergo pathological changes, and the compensation cannot take place normally; the right heart is soon overwhelmed by the quantity of blood running into it, and the consequence is a dilatation of the right auricle and right ventricle.

So the final results of an inspiratory and expiratory dyspnea are the same; they cause a dilatation of the right auricle and right ventricle, and finally disturb the whole cardiac system.

Add finally to all these causes of goiter-heart, the deleterious influence that almost any goiter has upon the cardiac fiber itself (this phase will be discussed more fully in the chapter devoted to Cardiovascular Symptoms in Thyrotoxicosis) then we shall better understand how goiter-heart is brought about.

Goiter-heart has an insidious development. The goiter may be present for many years before the patient is aware of the changes which are going on. For a long time the patient does not notice that the tone of the voice is changing and that he easily gets out of breath. He attributes the cause of all his troubles to chronic catarrh of the trachea and lungs. Later he complains of vertigo, headache, congestion of the face, epistaxis, palpitations, dyspnea at the slightest physical effort. At that time the volume of both cardiac chambers is markedly increased, caused by hypertrophy and dilatation.

In the early stages there is generally a slight systolic murmur to be heard at the apex, betraying a mitral insufficiency caused by the stasis in the small circulation. Later the second tone of the pulmonary valve becomes weak. In late stages systolic and diastolic murmurs may be heard on all its orifices. Arrhythmia appears. The liver, spleen and kidneys become congested; anasarca terminates the scene. By this time the pathological changes in the heart are so extensive and so irreparable that the entire therapeutic arsenal has become powerless.

Goiter-heart is not always present in all cases of stenosing goiter. The reason must be found in the resistance of the heart itself. It is a well-known fact in medicine that one heart may resist certain pathological conditions better than another. This is due to individual resistance and to the existence or non-existence of previous or concomitant intoxications or infections.

The influence of age certainly should not be neglected. Other things being equal, a young heart will offer more resistance than an old one. The majority of well-developed cases of stenosis, however, come on between the ages of forty and sixty; consequently the pathological changes in the heart are apt to be more severe at that period of life than in the earlier one.

The purely mechanical goiter-heart is not frequent. It is usually combined with thyrotoxic goiter-heart.

**The Thyrotoxic Goiter-heart.**—To this class we do not ascribe only the goiter-heart found in the well-developed exophthalmic goiter but also in all the intermediate stages.

As Wölfler says: "It is easy to go progressively from a simple goiter



to a well-marked Graves's disease: goiter with tachycardia; goiter with tachycardia and tremor; goiter with tachycardia, tremor and psychic disturbances; goiter with tachycardia, tremor, psychic disturbances, exophthalmos, etc., until we get the complete clinical picture of a well-developed Graves's disease." They are only different stages of the same process.

The thyrotoxic goiter-heart may be caused by any kind of goiter. The parenchymatous goiter is the most common cause, but a cystic or colloid goiter, even a cancerous or sarcomatous goiter, may give rise to a thyrotoxic goiter-heart. Cystic and colloid goiters do not cause a thyrotoxic goiter-heart as such, but their presence seems to incite the remainder of the gland to overfunction. In such cases the goiter becomes "Basedowified." The same explanation accounts for the rare cases in which exophthalmic symptoms develop in cancer or sarcoma of the thyroid gland.

The fundamental symptom of the thyrotoxic goiter-heart is the increased heart action. This symptom never fails. It is found in the fruste forms and may remain for a long time after the patient is practically cured of the other symptoms of exophthalmic goiter. In some cases the patient is not aware of the increased heart action, but in the great majority of cases he complains of palpitations. These may come on gradually or by spells. Oftentimes the slightest muscular exertion increases the action of the heart considerably. The pulse-rate may reach 120, 150 and frequently more.

The heart action is not only increased in frequency but in intensity as well. Often the whole cardiac region shows a pulsation, and the beating at the apex is strongly marked.

After a longer or shorter period of duration of the disease the heart area is increased. This increase, it is found, involves mostly the left ventricle. The apex beat is outside the mammillary line; the transverse diameter of the area of cardiac dulness is increased; fluoroscopic examination confirms these clinical findings. The heart lies transversely on the diaphragm. In a later stage when the thyrotoxic intoxication is far advanced the right ventricle shows a marked dilatation and the area of cardiac dulness is found extending 1, 2, 3 cm., and sometimes 4 cm., outside of the right sternal edge.

In many cases I have been surprised to find the difference in the area of cardiac dulness before and after exercise. Before exercise the heart limits were only slightly increased, but after exercise they were considerably enlarged. I consider this symptom very valuable before an operation to show the resistance of the heart to the surgical attempt. If after exertion dilatation of the heart is present, if the heart action increases considerably, and especially if myocarditis is present, one should "Pray the Lord and wait."

In thyrotoxic goiter-heart the pulse is frequently soft and dicrotism is often observed. In advanced cases the pulse may become irregular; blood-pressure may be increased, but not always however. When thyrotoxicosis is well developed the carotid arteries are distended and beat violently. The veins are enlarged, too, and show a venous pulsation. This vascular erethism is not due to the cardiac impulse, but seems to be merely localized in the vessels of the head and neck, because it does not extend to the abdominal aorta nor to the radial or other arteries. Oftentimes the patient feels the pulsation all over the head and complains of roaring in the ears. The cardiac impulse may be so intense as to shake the whole body synchronously with the heart beat.

Palpation of the neck shows a thrill, especially over the superior thyroid arteries. Auscultation frequently gives a systolic murmur not only just over the arteries but also all over the thyroid gland. This murmur, especially in the supraclavicular spaces, is sometimes continuous and forms what we call the "bruit de none." The thyroid gland shows not only a transmitted but also an expansive pulsation.

As a rule the mechanical goiter-heart and thyrotoxic goiter-heart are seldom separated clinically. Of course there are goiter-hearts which are purely of mechanical origin, but even then there exists between the mechanical goiter-heart and the thyrotoxic-heart a series of intermediary symptoms which are caused by the thyroid hyperfunction, and are consequently of thyrotoxic origin. Therefore the etiology of thyrotoxic goiter-heart and of Graves's disease is the same. There is no difference between the thyrotoxic goiter-heart described in the chapter on Graves's disease and the one complicating any colloid, cystic or malignant goiter. Goiter-heart disappears with thyroidectomy, or at least is greatly benefited, providing the operation takes place before the cardiac muscle has become irremediably altered.

These facts are of great importance. From them derives the first very clear indication: if a goiter cannot be cured, or at least held back in a harmless state by ordinary medical means, it should not be allowed to go on until a goiter-heart, toxic or mechanical, has made its appearance before performing thyroidectomy. Furthermore, these facts are of great diagnostic value and of great help to the surgeon in deciding if the operation can be done, also how and when.

When in goitrous tracheostenosis, the pathological disturbances in the heart and in the small pulmonary circulation have not damaged these organs to such an extent as to become permanent, surgical interference gives brilliant results. More than once I have seen cases of intrathoracic goiters with marked dyspnea, venous congestion of the cervical region, *irregular pulse*, headache, vertigo, etc., entirely relieved of all these symptoms after operation. The most remarkable case was

that of a woman with a totally intrathoracic goiter displacing the aorta and compressing the basis of the heart. This patient had what I thought was a marked degree of myocarditis. To my surprise, the day following the operation, the pulse had become regular and has remained so ever since.

But when a dilatation of the right heart has already taken place, when tachycardia, arrhythmia, congestion of the liver, spleen and generalized edema are present, an operation in such cases can only terminate by failure, and, what is worse, by death. This is so true that when Kocher reported the results of 3000 operations for goiter he said that the only real danger which he still feared in goiter operations was *cardiac collapse*. His advice was then to operate on a goiter as soon as possible and to discard any thyroid or iodine treatment when a goiter-heart was present.

## CHAPTER VIII.

### INTRATHORACIC GOITER.

WE call *intrathoracic goiter* a goiter which lies in the thorax. This variety of goiter may be *partially* intrathoracic or *totally* so. If we should call intrathoracic every goiter whose inferior poles dip more or less into the superior opening of the thorax, we should regard as intrathoracic many goiters not worthy of that denomination. Such goiters do not extend down into the mediastinal space; their inferior limits can be outlined more or less easily during swallowing or coughing. We apply to such a class of goiters the name *struma profunda* or *deep goiter* (Fig. 34) and reserve the term of *partially intrathoracic* (Figs. 31 to 35) to goiters whose greater portion lies in the mediastinal space and whose remaining portion lies in the cervical region. As the name indicates the *totally intrathoracic goiter* (Figs. 38 to 40) lies completely in the thorax; now and then there is not even external evidence of thyroid enlargement in the cervical region.

Intrathoracic goiter takes its origin either in the lower poles of the thyroid or in the isthmus; seldom does it develop in accessory thyroid glands. When originating from the lobes or isthmus the intrathoracic goiter remains, as a rule, connected with the body of the thyroid by a pedicle; if it develops from an accessory thyroid gland it has no relation whatsoever with the thyroid. These latter forms of goiter are rare. Intrathoracic goiter does not seem to develop oftener in the lobes than in the isthmus.

A goiter has a tendency to become intrathoracic for three chief reasons:

1. The thyroid gland normally goes up and down with respiration, with swallowing and coughing, hence the tendency to drop.
2. The goiter is more or less forced into the thorax by the various movements of rotation and especially flexion of the head.
3. By the natural action of gravity.

In short-necked people with a well-arched thorax the thyroid lies abnormally low, and a goiter developed in that gland is bound to become intrathoracic very soon. This abnormally low situation of the thyroid has been called by Kocher *thyroptosis* and is accompanied at the same time by a laryngoptosis. According to von Eiselsberg this thyroptosis is frequently found in patients with emphysema. Kreuzfuchs claims that, on the whole, an *isthmoptosis* is more frequently found



than a ptosis of the entire gland itself. In rare instances the isthmus seems to form a big body, *per se*, being connected with the lobes by only a thin bridge of connective tissue containing bloodvessels, and thus forming what Gruber calls *glandulæ tripartitæ*. In such glands the isthmus is very apt to sink into the superior opening of the thorax as soon as it grows in volume.

At first, a deep goiter extends only partly behind the sternum and underneath the first rib. It moves freely up and down with the larynx. Later, when the goiter has descended into the thorax and has grown more voluminous, it escapes out of the thorax only in forced respiration or coughing. But as the goiter continues to grow, there finally comes a time when it can no longer escape the superior opening of the thorax; it then lies in the superior mediastinal space and becomes more or less totally intrathoracic. In such conditions the up-and-down movements with the larynx have more or less lost their entire amplitude.

We can consequently conclude that the great majority of intrathoracic goiters have been at one time *cervical*. Only the ones which originate from an intrathoracic accessory gland, or which are developed at the cost of an extremely ptosed isthmus or lobe, are intrathoracic from the start. If two separate nodular goiters in the same individual become mediastinal they form a *double intrathoracic goiter*.

Intrathoracic goiters vary from the size of an egg to that of a large fist. They may be nodular and irregular in shape when they are formed by an aggregate of colloid nodules, but they may also have a smooth surface with a round or oval shape when formed by a cyst or by a unique colloid nodule. Histologically all the pathological varieties seen in simple goiter are found, too, in intrathoracic goiter.

That an ordinary goiter dips by its inferior poles more or less low into the superior opening of the thorax is seen quite frequently, and according to statistics and my own experience it occurs in about 25 to 35 per cent of all goiter cases; on the other hand, a partly intrathoracic goiter occurs in about 15 to 18 per cent of the cases. In this class, too, we find the *diving* or *plunging goiter* which has been so well described by the French authors and called *goître plongeant*. This plunging goiter may be median or lateral; it owes its name to the fact that at times it is cervical and at others intrathoracic. During coughing or forced expiration it springs up suddenly above the manubrium sterni and then disappears into the thorax again. Such goiter is liable to become incarcerated at the superior opening of the thorax and then cause very alarming suffocating spells. One of the most striking specimens of plunging goiter which I have seen was while I was the assistant to my master, Kocher. It was developed in a retroclavicular accessory thyroid gland on the right side, had no connection whatsoever with the thyroid, and with

each coughing used to play in the most exquisite way the game of "Now you see me; now you don't." In fact, it was the only symptom which had brought the patient to seek surgical attention.

Totally intrathoracic goiter includes all cases of goiter which lie in the thoracic cavity, showing no signs, more or less, of external enlargement of the gland. This is the *true intrathoracic goiter*. It occurs in about 6 or 7 per cent of the cases of goiter.

Intrathoracic goiter may in rare instances be congenital, but, as a rule, it is found in middle age about the fortieth year of life. My youngest case of totally intrathoracic goiter was a girl, aged about thirteen years, while my oldest was seventy-five years. It is more frequently found in men; it is of benign nature, but, of course, may undergo malignant degeneration. As ordinary goiter is by far more frequently seen in women than in men, it may seem peculiar to find intrathoracic goiter more frequent in men than in women. The reason is that men begin hard work very young and continue it all their life, more so than women. Hence the tendency for ordinary goiter to become intrathoracic.

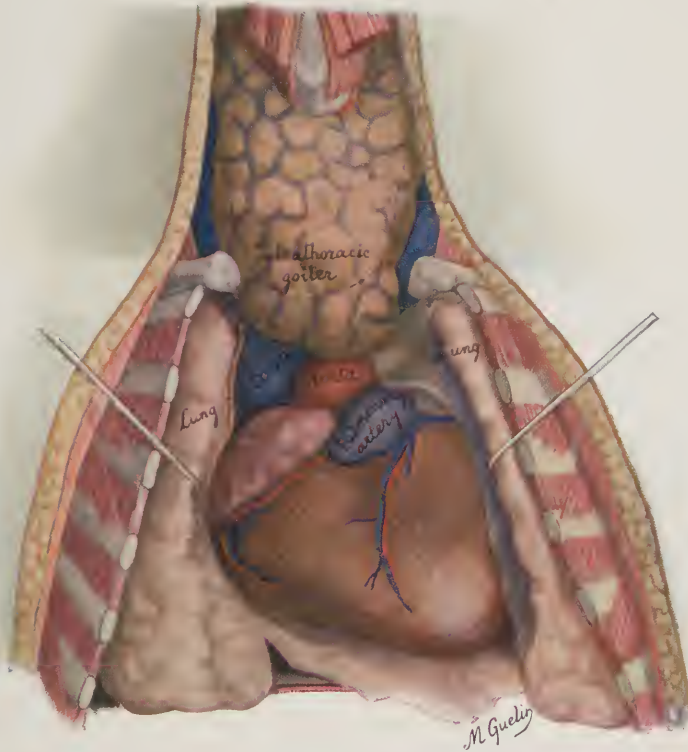
Intrathoracic goiter developed in the isthmus lies in the middle line and is called the *median intrathoracic goiter* (Plate VII, Fig. 1). A goiter developed in one of the lobes lies laterally of the middle line, and for that reason is called *lateral intrathoracic goiter*.

**Relation of Intrathoracic Goiter to Neighboring Tissues.**—The *median intrathoracic goiter* lies in front of the large vessels and is bounded by the manubrium sterni in front, by the trachea and esophagus behind, by the arch of the aorta or innominate artery below, and laterally by the lungs. The *lateral intrathoracic goiter* (Plate VII, Fig. 2) is bounded in front by a portion of the sternum, clavicle and costal cartilages, behind by the first three vertebræ with their costal insertions; inwardly by the trachea and esophagus; laterally by the pleural membrane; below by the arch of the aorta, the innominate, and the base of the heart; above, by the superior opening of the thorax. A very important relation of intrathoracic goiter is its relation to the large intrathoracic vessels; it may lie in front, which is less frequent, or behind them, or laterally too; the median intrathoracic goiter nearly always lies in front of these vessels. When situated behind the vessels it is called *retrovascular*; (Plate VIII, Fig. 2) when in front of them it is called *prevascular*.

From this it follows that an intrathoracic goiter comes in contact with very important organs, such as the right and left innominate artery and veins, the common carotids, the arch of the aorta, the base of the heart, the thoracic duct, both vagi, the inferior laryngeal, phrenic and sympathetic nerves, the trachea and the esophagus. On account of such dangerous vicinity it will be easily understood why an intrathoracic goiter may have a most striking symptomatology.

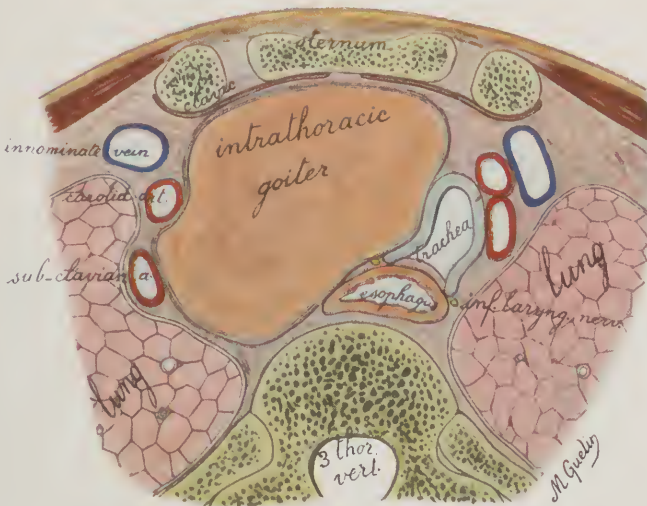
# PLATE VII

FIG. 1



Relation of a Median Intrathoracic Goiter to the Surrounding Structures.

FIG. 2



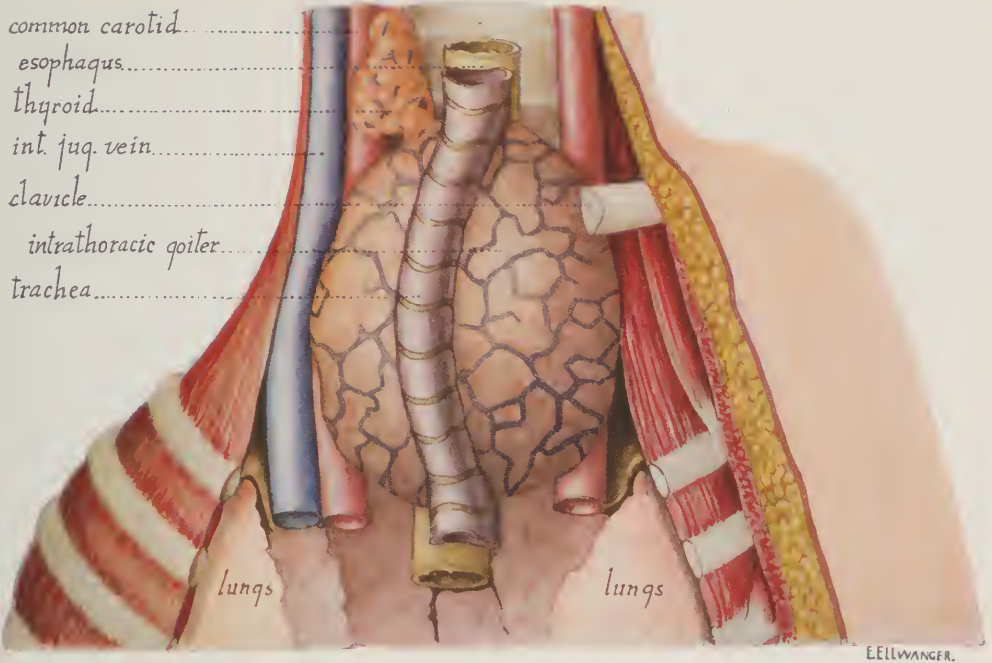
Cross-section of the Upper Part of the Thorax, Showing Relation of a Lateral Intrathoracic Goiter to Surrounding Structures.





# PLATE VIII

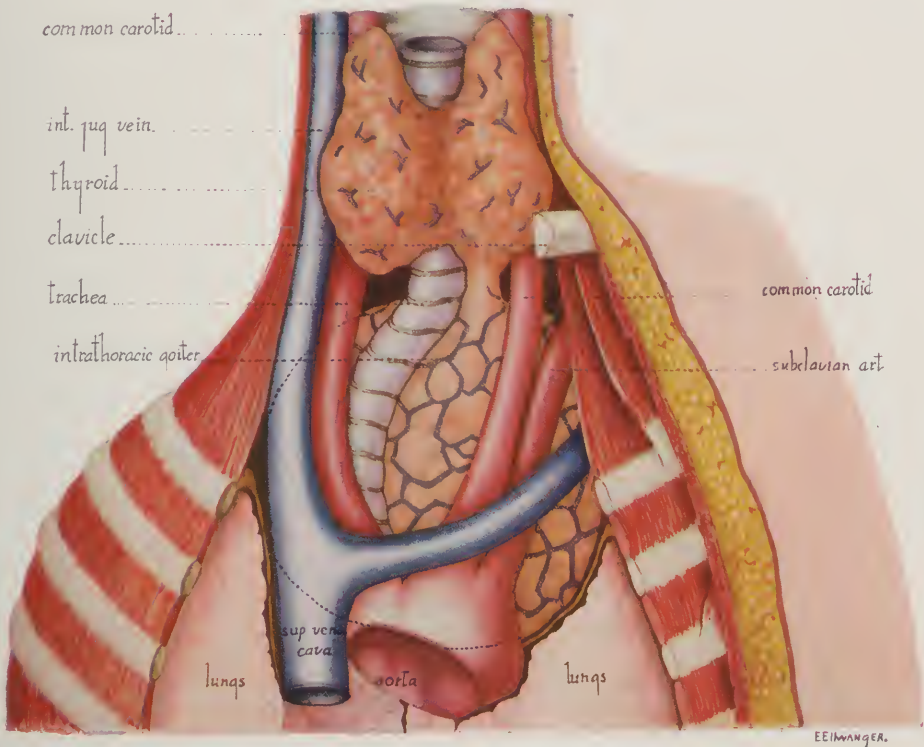
FIG. 1



Almost Totally Intrathoracic Goiter.

Note its unusual position, separating entirely the esophagus and trachea. The trachea is bent forward. Operated case. Recovery.

FIG. 2



Totally Intrathoracic Goiter.

Operated case. Recovery.



In intrathoracic as well as in cervical goiters the trachea may be displaced or compressed, or both together. If the pressure is of long standing the walls of the trachea may become atrophied. In median intrathoracic goiter, pressure takes place anteroposteriorly. In lateral intrathoracic goiter, pressure takes place laterally. If the windpipe is compressed laterally on each side by two nodular goiters, compression may be so marked that the two walls of the trachea may come in contact with each other and form what we call the *saber-sheathed trachea* (Fig. 26). If the two nodular goiters are at different levels then the trachea assumes an "S" shape (Fig. 27). Intrathoracic goiter may be found between the trachea and esophagus (Plate VIII, Fig. 1). Besides the trachea the goiter may exert pressure on one of the main bronchi. More seldom compression of the upper portion of the lungs may be found. In one of my cases compression on the right lung was so marked and had been of such long standing that gangrene of the apex followed and caused an empyema. All the large vessels of the thorax, even the superior vena cava, aorta and base of the heart, may undergo compression and displacement from intrathoracic goiter. (Plates VIII, IX). Thus, on fluoroscopic examination, the tumor may appear to pulsate and may then be taken for an aneurysm. Yet closer examination will show that this pulsation is not an expansive one but is only transmitted by the aorta or the other large vessels of the mediastinal space.

Injury to the inferior laryngeal nerve happens more frequently on the left than on the right side. Wölfler thinks this is due to the fact that the left inferior laryngeal nerve is more superficial than the right. That may be true in some cases; in others, however, Kienböck's explanation is more satisfactory. In his judgment, as the intrathoracic goiter presses and displaces the aorta toward the left side, it puts the inferior laryngeal nerve on the stretch, hence the injury to the recurrent nerve. This is to be expected, as we know experimentally that traction on the nerve is the equivalent of compression.

**Symptoms.**—The symptoms produced by intrathoracic goiter do not differ in any way from those described in conjunction with cervical goiter, except that they may be more intense and that suffocating spells may be caused by the slightest physical effort, or come on spontaneously, especially during the night. While in bed the patient cannot find a comfortable position for sleep as the recumbent position causes a congestion of the cervical region, soon followed by suffocation. On the other hand, pillows are of no use because they flex the head, causing the chin to press upon the goiter which, in turn, compresses the trachea, hence again bringing about suffocation. Such patients spend their nights in an arm-chair like asthmatic or cardiac patients. In one of my patients dyspnea was so marked that I had to operate on her in a sitting position, and had to keep her in that position until the goiter was fished

out of the thorax. When dyspnea is intense there is during inspiration a sucking-in of the suprasternal and the epigastric regions. This phenomenon is called by the French authors *tirage*.

In intrathoracic goiter the auscultative *findings* differ naturally with the situation, the volume and the relation of the goiter with the neighboring tissues. If a bronchus of secondary importance only is compressed, respiration in the corresponding portion of the lung will be diminished in proportion to the compression. If one of the main bronchi is totally compressed a complete *silence* will be found in all the corresponding regions of the lungs. If stenosis of the tracheobronchial tube is incomplete a loud, whistling inspiration and a prolonged expiration with tubular character will be found, especially over the sternum and on the spine. Emphysema and bronchial catarrh are of common occurrence. If the lungs themselves are compressed there is, in the area of pressure, diminished respiration accompanied with rough inspiration and prolonged expiration and tubular breathing. More than once such conditions have been considered as incipient tuberculosis.

Certain movements of the head increase dyspnea, whereas certain others afford an easier respiration. These facts soon become known to the patient, and it is not so rare to find a patient going about carrying his head always in the same set posture, as if he were suffering from a boil on the neck. When of long standing these abnormal positions may even produce secondary deformations of the skeleton. Krönlein, for instance, reported a case in which intrathoracic goiter had produced a scoliosis of the spine.

A symptom which is considered very valuable for diagnosis by Wölfler and Kocher is not only the displacement of the windpipe laterally, but also the ptosis of the larynx *in toto* and a reduction in its up-and-down movements: the radius of its excursions is reduced as if something were trying to hold it immobile. Laryngoptosis may sometimes reach such a degree that the cricoid cartilage lies at the level of the incisura sterni. *Fixation* and *ptosis* of the larynx are of great diagnostic value in intrathoracic goiter.

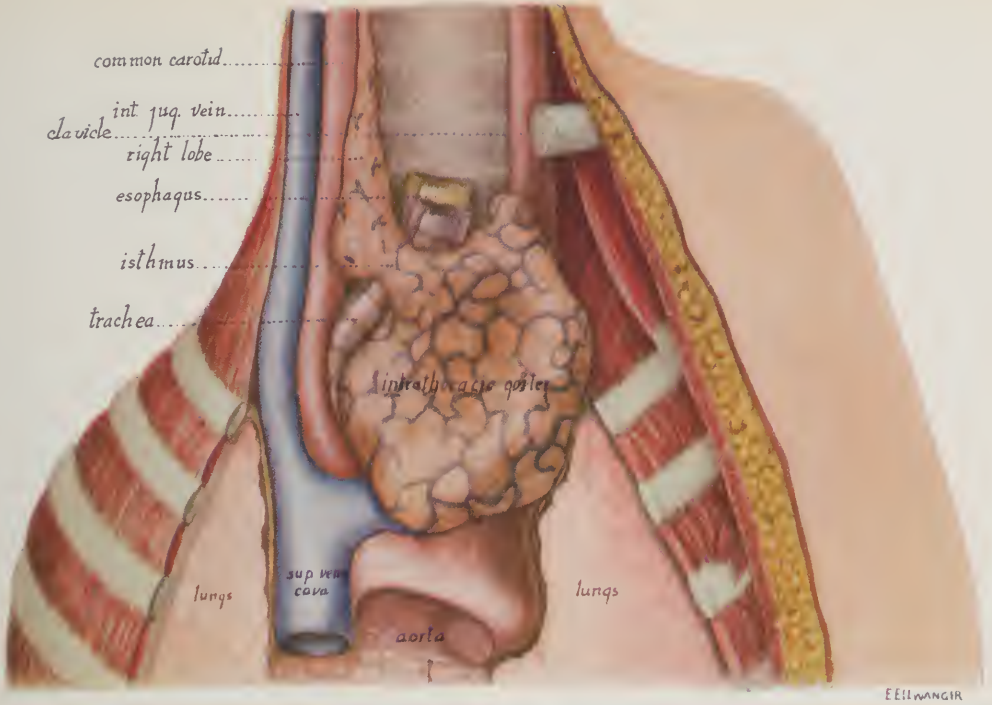
Symptoms of compression on the sympathetic nerve are much more frequent in intrathoracic than in cervical goiter.

Pressure on the subclavian and innominate veins and on the superior vena cava produces a congestion of the neck and head, hence roaring in the ears, vertigo, cyanosis, etc. In some cases the compression of the big venous trunks is so marked that the return flow to the heart is greatly impaired. In such cases a collateral circulation is established by means of the superficial veins of the thorax and inferior portion of the neck. These veins may sometimes attain enormous dimensions and be so numerous as to cover the entire upper portion of the thorax, form-



# PLATE IX

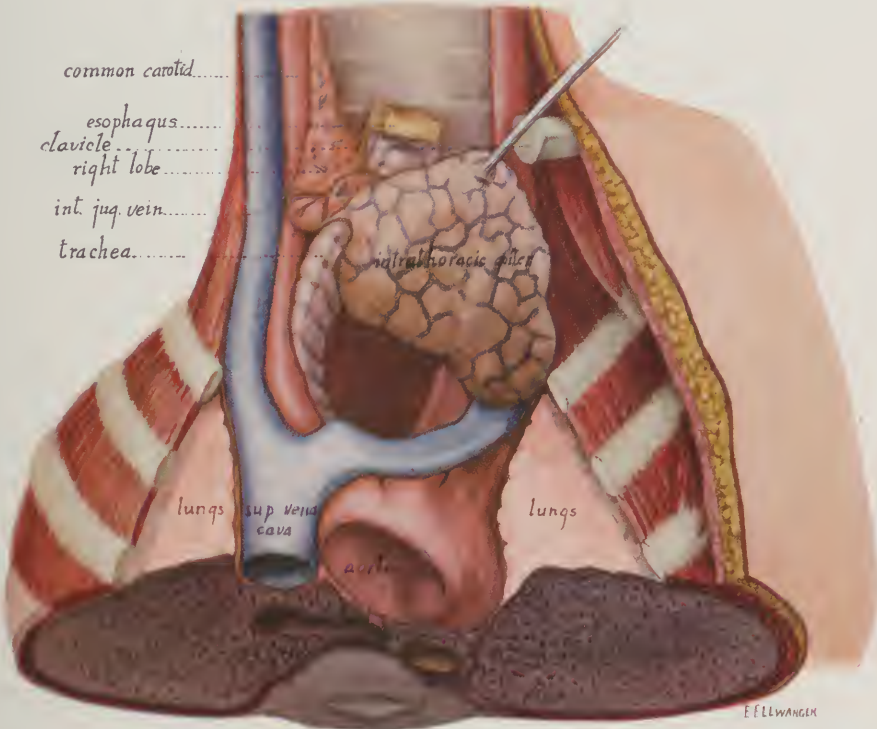
## FIG. 1



### Totally Intrathoracic Goiter.

Dissecting room finding due to courtesy of my friend, Dr. E. C. Buck, Professor of Anatomy, Ohio State University, College of Medicine.

FIG. 2



### Totally Intrathoracic Goiter, Reclined in Order to Show Its Anatomical Relation to the Mediastinal Organs.

Dissecting room finding due to courtesy of my friend, Dr. E. C. Buck, Professor of Anatomy, Ohio State University, College of Medicine.



ing what is known as the *caput medusæ* (Fig. 30). The blood seeks to reach the heart through the superficial anastomosis which joins the superior and inferior caval system, *via*, both azygos veins. The arm on the corresponding side may become edematous. In some rare instances compression on the large arterial trunks may diminish or suppress the pulsations of the carotid and radial artery on the side involved.



FIG. 30.—Partially intrathoracic goiter with a marked collateral circulation.



FIG. 31.—The goiter after its removal. The portion below the clavicle was intrathoracic.

To be exact, I must say that these symptoms produced by the interference of the arteriovenous system are not pathognomonic of intrathoracic goiter only, but are seen in any sort of mediastinal tumor.

The intrathoracic goiter more than any other goiter is apt to cause cardiac disturbances and give rise to what we call the *mechanical goiter-heart*, often combined with the *thyrotoxic goiter-heart*. This question has been thoroughly discussed in the chapter on Goiter-heart.

*Difficulty in swallowing* is found more often in intrathoracic goiter than in cervical goiter. These disturbances are caused not only because of compression but also on account of displacement of the esophagus. Pressure of long standing on the esophagus determines chronic inflam-

matory conditions in the musculature and in the esophageal mucous membrane, hence the difficulty and pain which the patient complains of in swallowing. Interference with the inferior laryngeal nerve, whose

branches partly supply the esophagus, may sometimes account, too, for much difficulty in swallowing.



FIG. 32.—Ten days after the operation.

Kreuzfuchs and other authors have described a symptom which is not pathognomonic for intrathoracic goiter alone, but is very often found in any other mediastinal tumor; it consists in the forward displacement of the manubrium sterni. Normally the manubrium and corpus sterni, although sometimes forming a slight angle, are on the same level. In intrathoracic goiter or any other mediastinal tumor the manubrium happens not infrequently to be displaced forward so as to form a

difference in the level between the manubrium and the gladiolus. This difference may vary from a few millimeters to a centimeter. If the cartilages of the first and second ribs participate, too, in this forward displacement the whole thing assumes a characteristic convexity often observed in malignant mediastinal tumors.

*Dulness* over the sternum is always present, except in the few cases in which the intrathoracic goiter is of very small size and covered by emphysematous lungs. Gentle percussion is best suited to bring out the outlines of intrathoracic goiter. As a rule a dulness with a downward convexity will be found, a point of good differential diagnostic value, as in aneurysm this dulness will rather show an upward convexity. X-rays are, of course, of paramount value. Another symptom of great diagnostic value is the displacement of such dulness by forced respiration: it goes downward with deep inspiration and upward with expiration. As a rule the dulness over the sternum is smaller than the goiter itself, because the concomitant emphysema which is always present in tracheostenosis prevents the outline of the true limits of the tumor. In lateral intrathoracic goiter dulness is localized over the manubrium sterni, over the cartilages of the second, possibly of the third rib, and over the sternoclavicular articulation; the side will depend upon which side the goiter has originated. If the intrathoracic goiter is median the dulness will be found mostly over the manubrium sterni.



In normal individuals *auscultation* over the manubrium sterni will, as a rule, show a faint *indication* of respiration or no respiration at all. But if an intrathoracic goiter is interposed between the sternum and the trachea, and with still greater reason if the trachea is compressed, auscultation over the manubrium sterni, as a rule, will reveal a loud inspiration and a prolonged expiration accompanied with marked tubular breathing.

*X-ray examination* should really become a part of the routine examination in any suspected intrathoracic goiter. It not only confirms the clinical findings, but completes them. Sometimes, when it is difficult to decide on which side of the thorax the intrathoracic goiter is located, *x-rays* will show it. The fact that there is a double intrathoracic goiter may escape clinical detection; the *x-ray*, however, will nearly always give one this information. Furthermore, it gives precise indication on the situation, form, etc., of the trachea. Finally, it may prevent the surgeon from overlooking conditions of the thoracic organs, which may have great influence on the success of the operation, such as tuberculosis, pleural exudate, etc.

Normally, in the dorsoventral roentgenogram, the shadow may be divided into three parts: a cervical, a mediastinal and a cardiac shadow (Figs. 33 to 40).

In intrathoracic goiter the shadow of the cervical and mediastinal portion is much increased. Laterally the shadow may reach the inner third of the half of the clavicle. Downward it may cover the base of the heart, extending to the middle of the manubrium sterni and to the cartilage of the third rib. Upward, when the goiter is partially intrathoracic, it extends and fuses with the shadow of the cervical goiter. The tone of the shadow of the intrathoracic goiter, as a rule, is regularly distributed, dark and opaque; its contour is convexed laterally and sharply marked, as a rule, because of the contrast with the shadow of the lungs, which is clear. Instead of being regular and convexed, however, the contour may be undulated and irregular, indicating a nodular goiter or a malignant tumor. The shadow of the aorta and of the vena cava may be absolutely covered by the goiter, and not uncommonly the arch of the aorta is found displaced toward the left side and downward.

The shadow of the intrathoracic goiter may be median or lateral. In the median the trachea is absolutely covered by the goiter and no shadow of the windpipe is seen in the roentgenogram. In the lateral intrathoracic goiter the shadow is mostly developed on the right side or on the left side of the mediastinal space, according to the position of the goiter. In that case the aorta may be seen displaced toward the left side. The windpipe may be followed more or less in its entire course and

may be displaced or compressed or may be both together. In a few instances the trachea may be followed to its bifurcation.

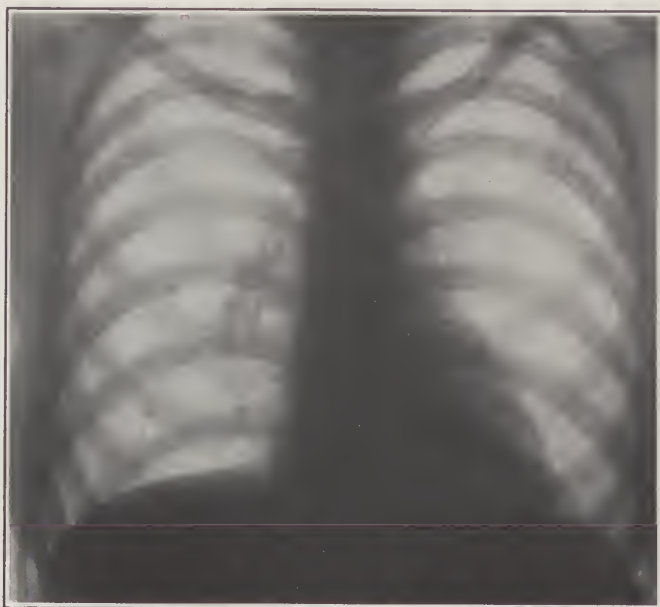


FIG. 33.—Normal roentgenogram of the mediastinal space.



FIG. 34.—Roentgenogram of a struma profunda or deep goiter.

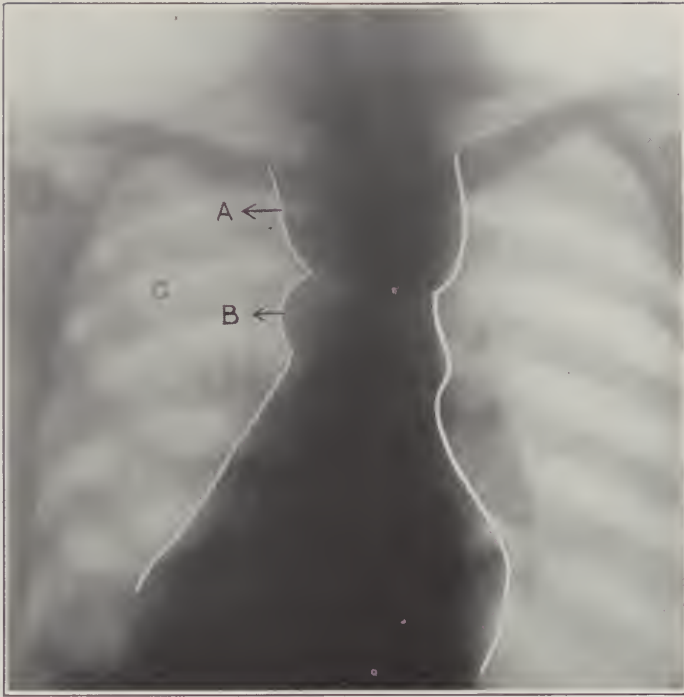


FIG. 35.—Roentgenogram of a partially intrathoracic goiter. *A*, intrathoracic goiter; *B*, aorta.

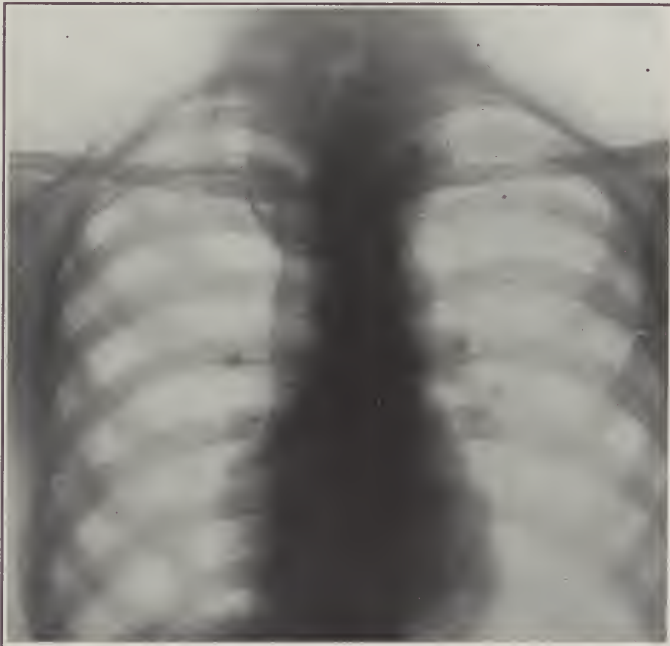


FIG. 36.—Roentgenogram of a partially intrathoracic goiter. Note compression and displacement of the windpipe.



FIG. 37.—Roentgenogram of a partially intrathoracic goiter.



FIG. 38.—Roentgenogram of an almost totally intrathoracic goiter from patient, Fig. 39.



In intrathoracic goiter not only roentgenography but fluoroscopy is of the utmost importance. A fluoroscopic examination will reveal the pulsations, the up-and-down movements of the goiter during inspiration and



FIG. 39.—Almost totally intrathoracic goiter. Note youth of patient (fourteen years).

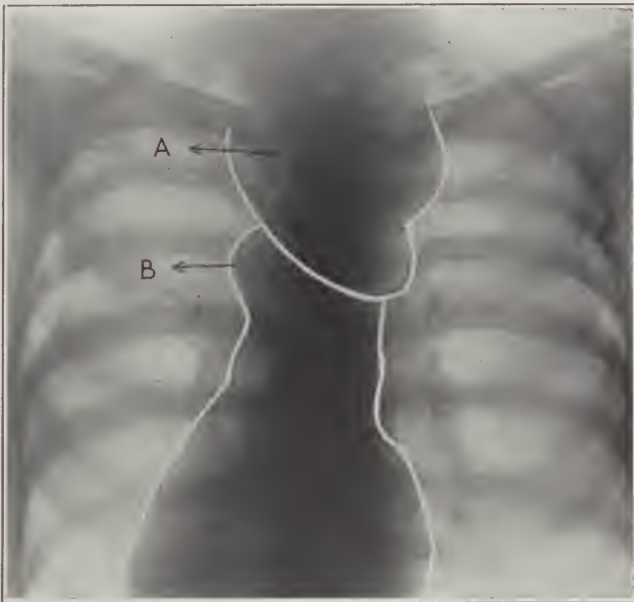


FIG. 40.—Roentgenogram of a totally intrathoracic goiter: *A*, intrathoracic goiter; *B*, aorta. The goiter after removal is shown in Fig. 41.

deglutition. The shadow of the goiter is not infrequently seen pulsating; these pulsations, however, are not expansive but are transmitted from the neighboring large vessels, especially from the aorta.

Up-and-down movements synchronous with the act of swallowing are pathognomonic of a tumor developed in the thyroid gland. This symptom never fails, except in an abnormally large incarcerated intrathoracic goiter or in malignant degeneration. On the fluoroscopic screen the goiter is clearly seen rising with the trachea and larynx, but the aorta remains immobile. In a few instances the aorta is seen rising with the goiter; this does not mean, however, that the aorta is adherent to the goiter, but only that the pressure from the goiter on the aorta being released, the normal elasticity of the aorta brings this large vessel into its normal position again. The best way to observe these up-and-down movements is to have the patient swallow water, or, better, to have him take a very deep inspiration, hold it for a few seconds and then perform a quick expiration. In so doing the intrathoracic goiter goes downward during deep inspiration and comes upward with expiration. Sometimes, according to Kreuzfuchs, a small intrathoracic goiter located behind the manubrium sterni or behind the sternoclavicular articulation may escape notice on the roentgenogram, but becomes fluoroscopically detectable while the patient is taking a deep inspiration, because the nodule emerges laterally from the shadow of the sternum.

**Diagnosis.**—The diagnosis of a partially intrathoracic goiter is, as a rule, not difficult. Usually we have to deal with a patient who has had a goiter for a longer or shorter period of time. He complains of dyspnea and palpitation, and more recently may have had spells of suffocation. We find a cervical goiter. Our first duty is to outline its inferior limits. If we do not succeed we ask the patient to cough or to swallow. In that way, if the goiter lies only behind the episternal notch, the palpating finger will be able to outline its inferior limits; but if the goiter extends farther down we shall not know how far down the goiter reaches. We shall have to rely upon percussion and auscultation. We must see if there is any congestion or puffiness of the face; if there is any collateral circulation in the neck, thorax and arms; if there is any difference between the radial and carotid pulse on each side; if there is any irritation or paralysis of the sympathetic nerve; any fixation or ptosis of the larynx; any displacement of the windpipe, or any difficulty in swallowing, etc. These symptoms and the  $x$ -ray picture will terminate the examination, and as a result diagnosis of partially intrathoracic goiter will always be made. But with a goiter which is totally intrathoracic, diagnosis is very much more difficult. Here we shall have to rely mostly upon the *mediastinal symptoms*.

The first thing to do is to ascertain that the thyroid gland is in its normal position and that the two lobes and isthmus are normally situated, since a missing lobe is a feature of enormous diagnostic value. In the latter condition, Wührmann claims that there is a depression of the skin between the sternocleidomastoid muscle and the larynx.

Another symptom of great importance is the feeling with the finger of an impact above the episternal notch during expiration, swallowing or coughing. This impact is caused by the intrathoracic goiter rising with the larynx.

The presence of a pedicle extending from one lobe or isthmus downward behind the sternum is a clue of great diagnostic value. If, furthermore, the palpating finger is not able to feel, as is normally the case, the tracheal rings of the windpipe behind the episternal notch, but finds, on the contrary, a mass interposed between the sternum and the trachea, and if this mass moves up and down during swallowing, the diagnosis of an intrathoracic goiter is certain. But such symptoms as those above mentioned may not be present, or may be doubtful, and then the diagnosis becomes greatly difficult. In such cases we must decide:

1. Whether we have to deal with a mediastinal tumor, and if so,
2. What is its nature?

That we have to deal with a mediastinal tumor will be shown by the subjective symptoms described by the patient, as well as the objective ones found in the course of our examination, such as congestion; puffiness of the face and neck; collateral circulation of the thorax; diminution or disparation of the radial pulse on one side; possibly edema of one arm; well-defined dulness over the upper portion of the thorax; forward displacement of the manubrium sterni; paresis or paralysis of one or both inferior laryngeal nerves, and an unmistakable shadow on the roentgenogram. These mediastinal symptoms will not always be all present, but in the great majority of cases there will be enough of them to warrant a sure diagnosis.

When once the diagnosis of mediastinal tumor is made with certainty we must decide if we have to deal with an intrathoracic goiter or not. In that direction the history of the patient may furnish precious indications. He may have previously had a goiter which has "disappeared." Indeed, it is not infrequent to see patients who believe that they have been cured of a goiter because their neck seems to be free from it; nevertheless the goiter is still present but has become intrathoracic.

The symptoms which will be of great value in deciding if a mediastinal tumor is a goiter or not are:

1. Dyspnea, which is entirely out of proportion to the cervical goiter, if there is any, or with the size of the mediastinal tumor, as shown by the roentgenogram and percussion. The suffocating spells, especially at night, speak for goiter, as also does the fact that flexion, or extension, or lateral movements of the head increase dyspnea or cause suffocation. These suffocating spells may be stopped or greatly benefited by pulling the larynx upward or by displacing it laterally; on the contrary, in con-

ditions other than goiter these procedures usually accentuate the suffocating spell.

2. A ptosis of the larynx and diminution of the radius of its excursions or its entire fixation. In mediastinal tumors other than intrathoracic goiter, ptosis and fixation of the larynx are less frequently seen



FIG. 41.—Totally intrathoracic goiter.

3. The absence in the cervical region of one lobe or the isthmus (Figs. 41 and 42). This symptom is of great diagnostic value.

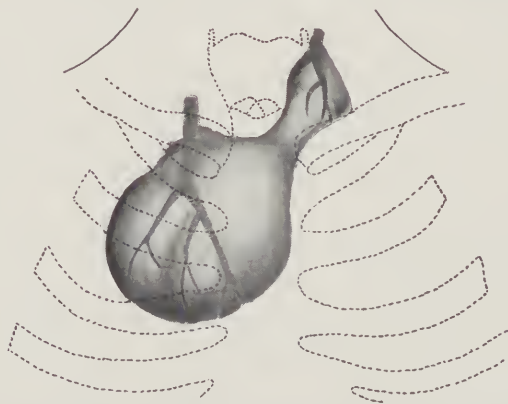


FIG. 42.—Intrathoracic goiter accompanied with thyro- and isthmoptosis.

4. The feeling of an impact behind the episternal notch when the patient swallows.



5. Stenosis of the trachea in the region of the fifth, sixth or seventh cartilaginous rings of the trachea, detected either by laryngoscopy or tracheoscopy.

6. If symptoms of hyperthyroidism are found in connection with this mediastinal tumor, as tachycardia, tremor, exophthalmos, nervousness, etc., the chances are great that we have to deal with an intrathoracic goiter.

7. The fluoroscopic examination will be of enormous value, especially if it is able to show the up-and-down movements of the shadow synchronous with the act of swallowing. In that case the diagnosis becomes certain.

**Differential Diagnosis.**—Sometimes the difficulty is to decide whether we have to deal with an *aneurysm* or an intrathoracic goiter, since even fluoroscopic examination will not always solve the problem. Symptoms may be much the same in both cases, pulsations being transmitted to the intrathoracic goiter by the innominate or the arch of the aorta. These two conditions have been mistaken one for the other more than once. It would seem that in doubtful cases auscultation of the heart and aorta would throw the necessary light upon the diagnosis, yet it is not always so, as auscultation of an aneurysm may be entirely negative.

Here the physical and roentgenographic examination will be of great help. If the shadow is located more or less to the left of the mediastinal space the diagnosis between aneurysm and intrathoracic goiter is most difficult; but if it is located to the right, and if sympathetic and laryngeal nerve symptoms are present on the right side, too, the chances are great that we have not to deal with an aneurysm, but with a goiter, unless we should be unfortunate enough to meet with an aneurysm of the innominate. Each of the symptoms above mentioned should be given careful attention and its relative value duly considered in order to arrive at a safe diagnosis.

Kreuzfuchs says that a shadow of an intrathoracic goiter differs from the shadow of an aneurysm by the fact that there is an angle between the shadow of the vessels and the tumor, and that at the fluoroscopic examination during the act of swallowing these two shadows separate from each other in the case of goiter. If it were always possible to determine on the fluoroscopic screen, if pulsation seen in the tumor is an *expansile* instead of a *transmitted* one, diagnosis would then be made easier, because we know that an aneurysm expands in every direction; whereas in transmitted pulsations such a movement takes place always in the same direction. Unfortunately this is not always possible. More than that, one may come against cases of true aortic aneurysm where *no* pulsations whatsoever can be detected, because the aneurysm happens to be accompanied by diffuse inflammatory or syphilitic medias-

tinitis. Lateral fluoroscopic examination is of great help in deciding if we have to deal with an aneurysm or a mediastinal tumor, because in the latter conditions there is no *clear space* between the spine and the tumor, whereas this "clear space" exists in aneurysm (Figs. 43 and 44) unless the aneurysmal sac has acquired large dimensions and a peri-aortitis, due to frequent hemorrhages, has taken place.

A large and flat aorta might be mistaken for a mediastinal tumor, but in that case a lateral view of the patient will clear up the diagnosis.

*Syphilitic* or *tuberculous mediastinitis* must be differentiated from the intrathoracic goiter. Both varieties of mediastinitis are located mostly in the posterior superior mediastinum, whereas intrathoracic goiters are seen in the superior anterior mediastinum. Roentgenographic examination shows that in mediastinitis the shadow is more diffuse and somewhat

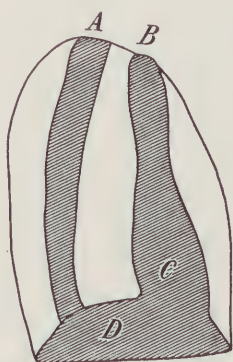


FIG. 43.—Lateral roentgenogram of a normal heart: A, spica; B, aorta; C, heart; D, diaphragm.

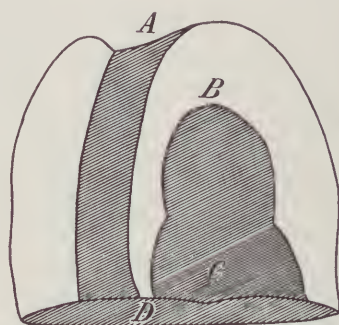


FIG. 44.—Lateral roentgenogram of an aneurysm.

linear, whereas the shadow of a goiter is more curved and convex downward. In tuberculosis of the mediastinal space the roentgenogram will show enlarged tracheobronchial glands at the hilum of both lungs. In syphilitic mediastinitis (Fig. 45) Wassermann and specific treatment may clear up the diagnosis.

*Hypertrophy of the thymus* may have to be differentiated from an intrathoracic goiter. This thymic hyperplasia occurs mostly during the early years of life. However, in adults it may persist and is especially found in combination with goiter. The *x-ray* picture of thymus hyperplasia is absolutely different from the picture of intrathoracic goiter. The diagnosis of thymus hyperplasia, contrary to all that has been written, is possible in a great majority of cases. Clinical examination must be always accompanied by this roentgenographic examination.

Normally a roentgenographic mediastinal shadow (Fig. 33) measures

from 2.5 to 3.5 cm. under the arch of the aorta, from 3 to 3.5 cm. at the arch of the aorta, and from 5 to 6 cm. at the conus arteriosus. The shadow of this region is dark, opaque and regularly distributed, and has definite limits.

In *thymus hyperplasia* there is a shadow which overlaps laterally the normal mediastinal shadow (Figs. 46 and 47). It may affect one lobe more than the other, or may affect both lobes in the same proportion. The thymic shadow is more or less triangular. From the base of the heart it extends upward on each side in a straight line or follows to some



FIG. 45.—Syphilitic mediastinitis. Note the location of the shadow.

extent the contour of the mediastinal shadow; it covers the auricles, which seem to be overdistended, and forms an angle between them and the ventricles; hence, too, an enlargement of the auricles which is not in proportion to the rest of the heart. The character of this thymic shadow differs from the cardiac and mediastinal shadows. It is thin, transparent, soft and regularly distributed; its edges, as a rule, are sharply limited and linear.

**Prognosis.**—The prognosis of an intrathoracic goiter depends upon many factors. A lateral intrathoracic goiter may sometimes cause

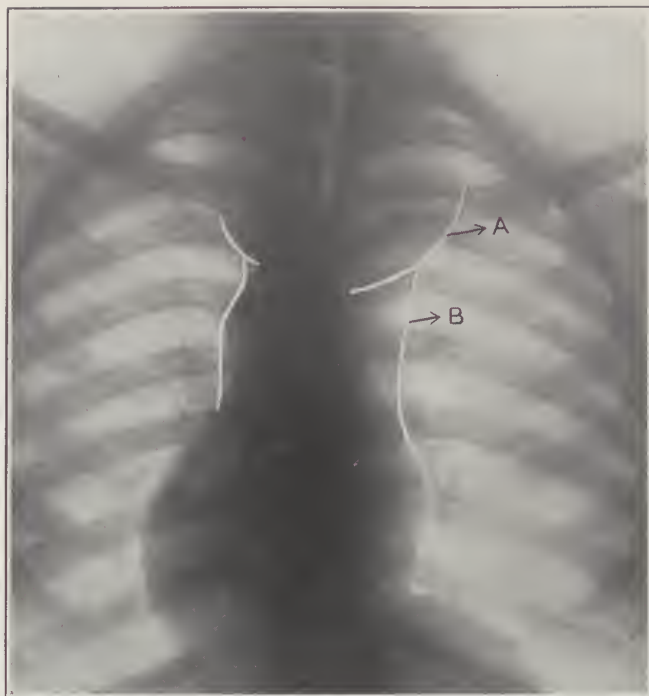


FIG. 46.—*A*, intrathoracic goiter; *B*, thymus hyperplasia. Findings corroborated by postmortem.



FIG. 47.—*A*, thymic shadow.



pulmonary symptoms. A median intrathoracic goiter will compress the trachea anteroposteriorly, and consequently give dyspneic symptoms much earlier than the former one. Compression of the windpipe and of the bronchial tubes causes a stubborn catarrh which resists every medical treatment. Intrathoracic goiter more than any other is apt to cause choking spells, but one of the most tragic terminations of an intrathoracic goiter is "sudden death," which will be discussed in the chapter on Goiter Death.

Even free of symptoms, an intrathoracic goiter is still dangerous to the patient because a hemorrhage may take place, or an acute infection or a malignant degeneration may develop in it and so endanger the life of the patient.

In skilful hands the prognosis of the cases treated surgically is excellent. Out of his last 77 cases of intrathoracic goiters, Kocher lost but 1 case. Autopsy showed advanced sclerosis of the coronary arteries of the heart.

## CHAPTER IX.

### GOITER DEATH.

IN patients suffering from tracheobronchial stenosis, any congestion of the respiratory apparatus or any physical exertion increases the shortness of breath; even talking taxes their strength to the utmost, and it is not unusual for them to stop in the middle of a sentence to get breath: inspiratory stridor is then, more or less, always present. With a little care, however, such patients may get along for years without choking spells, inasmuch as they adapt themselves to the smaller caliber of the trachea and to the diminished oxygenation of the blood. Yet, disregarding the fact that such patients are more liable than others to have pneumonia, their lives are otherwise always endangered because a slight catarrh, or any other trifling cause, may determine a dangerous choking spell which may terminate in death.

*Sudden death* is one of the most tragic and often one of the most unexpected endings of those afflicted with goiter, especially with the intrathoracic variety.

One who has seen many goiter patients with choking spells knows, for instance, that these patients learn by experience that twisting of the head in certain ways increases dyspnea, whereas carrying the head in some definite manner makes respiration easier, because in so doing they unconsciously relax certain muscles, thus diminishing the direct pressure upon the goiter, which in turn allows respiration to take place more freely. If, however, during sleep they should make a false movement of the head so as to twist or compress the trachea, they at once awaken in need of air and try to find again the stereotyped position in which respiration is easier. If they succeed, all well and good: the spell will soon be over. But if they do not, and if there is at the same time a congestion of the larynx and a catarrhal condition of the windpipe, and if there is added to this as the consequence of congestion an active and passive venous stasis in the goiter, which results in an increased volume of the goiter itself, and in turn in an increased pressure on the windpipe, then the efforts of the patient to get his breath are useless: the tracheal stenosis has become complete and death must ensue.

As said before, these choking spells occur most frequently with all forms of intrathoracic goiter; among them the *plunging goiter* must be given special consideration. As we know, this goiter has a long pedicle,

and has a wide range of excursion, since it can wander from the cervical region into the mediastinal space, and *vice versa*. Suppose, now, that a sudden hemorrhage, or that an active or passive venous congestion takes place in that goiter, then at once the latter increases in size, and on that account can no longer escape the superior opening of the thorax: it becomes *incarcerated* behind the sternum. The tighter the incarceration the more marked are the congestive symptoms, hence increased pressure upon the windpipe, hence suffocation and death. In fact, any sudden increase in the volume of any form of goiter is liable to cause sudden death. In pregnant women during delivery the violent efforts of expulsion cause an intense swelling of the goiter, which in turn compresses the windpipe. The same is true of sudden hemorrhages or acute infections taking place in colloid or cystic goiters. The same is true, too, of these intense venous congestions occurring in goiters of newborn babies. All these deaths occur by the same mechanism, namely, by the compression of the windpipe. This process is made worse by the spasmodic contraction of the cervical muscular belt, especially that of the sternocleidomastoid muscles acting as auxiliary muscles of respiration during the dyspneic spell. In such conditions the goiter plays the part of a hard ball pressed violently against the trachea. This is especially true in cases in which the cervical musculature has not yet undergone atrophy.

In some cases pressure on the windpipe and on the venous trunks is only moderate; the laryngotracheal catarrh is not marked; the inferior laryngeal nerves are not traumatized, yet during menstruation, pregnancy, physical effort, or on account of an increase in the volume of a goiter due to hemorrhage or infection a sudden hyperemia and congestion of the laryngeal mucous membrane take place and *edema of the glottis* follows. The patient becomes cyanotic and fights for air; this suffocating spell may soon be over or may terminate in death. This form of sudden death has been especially observed in pregnant women, very likely because the renal filter in pregnancy is often at fault.

But there are cases of sudden death in which there is no compression at all, where there is no softening of the windpipe, where the bronchial or tracheal catarrh is absent, where the renal function is normal, and where the cervical muscular belt has no murderous intentions, yet the patient dies suddenly of suffocation. "This acute choking spell without any tracheal stenosis surprises the patient," says Krönlein, "without warning, like a thief in the night." The patient may previously have had a slight shortness of breath or may have been entirely well; his voice may have been entirely clear; he may have been sleeping quietly, when suddenly he wakes and rushes to the window to get fresh air. He can scarcely speak, and a long whistling stridor shows that the

patient is in danger of choking. From this spell he may recover in a short time or he may not.

In such conditions death is due to the *spasmodic contraction of the glottis*, through stretching of or pressure on the inferior laryngeal nerve by the goiter. As Kraus and Krishaber have shown, the choking spell due to compression of the inferior laryngeal nerve is not at all caused by paralysis of the nerve but by its excitation. When the nerve is paralyzed there is no longer danger of glottic spasm. Indeed, we know that the dilatators as well as the constrictor muscles of the glottis are all supplied by the inferior laryngeal nerve. But we must remember, too, that the constrictors, being stronger than the dilatators when irritation of the recurrent nerve following pressure takes place, closure instead of dilatation of the glottis occurs: hence *spasm of the glottis*. And let us not forget that pressure on the inferior laryngeal nerve does not need to be bilateral in order to cause this spasmodic condition, because the arytenoid muscle is an unpaired muscle. As Dieulafoy rightfully says, "This muscle, which arises from the posterior surface and outer border of one arytenoid cartilage and is inserted into the corresponding parts of the opposite cartilage, always has the same effect, namely, that of bringing its two insertions together when it contracts, thus closing the glottis." It is the only muscle in the organism which exerts its action simultaneously on both sides of a symmetrical organ. Accordingly, excitation of one of the recurrent nerves will determine, on the one hand, constriction of the interligamentous glottis by the action of the lateral crico-arytenoid muscles and of the thyro-arytenoid muscle on the corresponding side, and on the other hand the complete occlusion of the respiratory glottis by the bilateral action of the arytenoid muscle. Respiratory and vocal troubles result from this combined action.

There are, however, cases of goiter death in which the laryngoscope shows an absolutely normal function of the vocal cords; the voice is normal; there is no sabre-sheathed trachea; compression of the wind-pipe is only moderate; symptoms of bronchial catarrh are lacking, and no plunging goiter can be incriminated, yet the patient suddenly drops dead without a sign of warning. Death occurs without a struggle. This is the "*Tod ohne kampf*" of the Germans and "*la mort sans phases*" of the French. In such conditions death is absolutely unexpected; the patient, while talking, reading or drinking, suddenly dies. It is a *goiter-heart death*; the heart simply stops. Of course tracheotomy is useless and medicine is powerless in the presence of such a tragedy. Postmortem will show a dilatation of the right ventricle, and dilatation and hypertrophy of the left ventricle, *fatty degeneration* of the cardiac musculature, *brown atrophy* and *myocarditis*. These are the causes of death.



## CHAPTER X.

### CIRCULAR GOITER.

THE circular goiter is a goiter which surrounds more or less completely the trachea, or both the trachea and esophagus (Figs. 48 and 49). The inner portions of both lobes of the thyroid gland grow gradually inwardly until they come in contact, one with the other, thus forming a ring of glandular tissue in which the esophagus and trachea are caught (Fig. 50). Such goiters are found in the newborn as well as in adults, and are mostly of parenchymatous nature.

**Symptoms.**—Among the most striking symptoms caused by a circular goiter are dyspnea and dysphagia. On account of its anatomical relations, this form of goiter is easily liable to cause disturbances of the inferior laryngeal nerves. It also frequently causes sudden death. Circular goiter does not need to be very large to cause dyspneic symptoms. In 1854 Maurer reported a case of a child who was suffering from dyspnea. Examination of the neck did not present anything abnormal, yet postmortem revealed a small circular goiter encircling the trachea. While demonstrating anatomy at the Ohio State Medical College in 1915, I found a most striking example of circular parenchymatous goiter. The gland *in toto* was scarcely more than twice its normal size. From the inner and posterior angle of each lobe there sprang at sharp angles laminæ of thyroid tissue which passed behind the esophagus and came in contact with each other. I was unable to ascertain if during the life of the patient symptoms were present.

**Diagnosis.**—Diagnosis is not always easy. When a parenchymatous goiter of moderate size causes dyspneic symptoms which seem to be



FIG. 48.—Congenital goiter. Natural size. Anterior view.

out of proportion to the size of the goiter, and especially when one or both inferior laryngeal nerves are involved, the possibility of a circular goiter should never be overlooked. Palpation may convey the

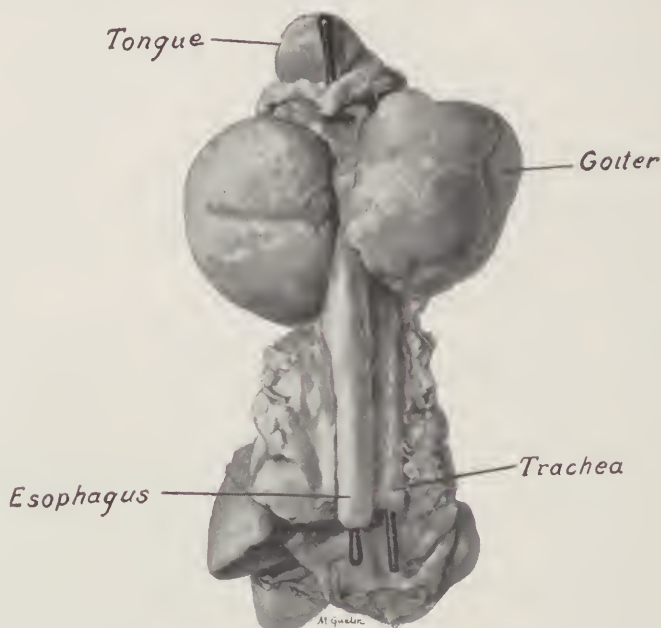


FIG. 49.—Circular goiter surrounding the trachea and esophagus. Autopsy of a newborn. Natural size. Posterior view.

impression that the lobes of the thyroid seem to disappear behind the esophagus and windpipe. Laryngoscopy, tracheoscopy and esophagoscopy may reveal a circular compression of the esophagus and windpipe.

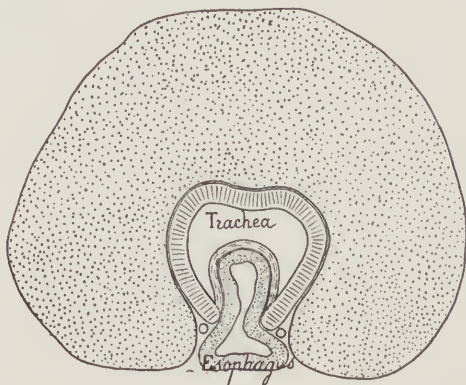


FIG. 50.—Pressure upon windpipe and esophagus by a circular goiter.

**Treatment.**—The treatment of circular goiter must be surgical. Great care should be taken to avoid injuring the inferior laryngeal nerves.

**RETROTRACHEAL OR RETROESOPHAGEAL GOITER.**

This variety of goiter is developed at the cost of an accessory thyroid nodule, and is located behind the esophagus or windpipe. It is entirely independent of the main body of the thyroid. This form of goiter is rare and the main symptoms which it causes are dyspnea and dysphagia.

**INTRATRACHEAL GOITER.**

Intratracheal goiter is very uncommon. Women are much oftener afflicted than men, and every recorded case has occurred between the ages of twelve and thirty-five years. The only symptom which brings the patient to the physician is an increasing dyspnea which may develop quite rapidly in a few weeks or may take a slower course.

Laryngoscopy and bronchoscopy are the only two means of making a correct diagnosis. A subglottic tumor will be seen filling, to greater or lesser extent, the lumen of the trachea. It may be round, cylindrical or oval in shape, with smooth surface, and covered by an intact mucous membrane. It is implanted by a broad basis on the tracheal wall. Its average size is about 2.5 cm. in length to 1.5 cm. in thickness, and it is nearly always located in the upper part of the trachea between the cricoid cartilage and the first five tracheal rings. Radestock, however, reported a case in which postmortem showed the tumor located at the mouth of the right bronchus. Intratracheal goiter does not seem to show predilection for any special portion of the walls, since it is found in the anterior, posterior and lateral walls of the windpipe.

Suspicion of an intratracheal goiter will be aroused when dyspneic symptoms cannot be accounted for. If, in a young individual complaining of dyspnea, laryngoscopy and bronchoscopy show a subglottic tumor with smooth surface, round or cylindrical in shape, and with a broad basis, the diagnosis of intratracheal goiter can be made with great probability. As said before, the site of the tumor on the walls of the trachea is of no diagnostic value. Differential diagnosis will have to be made with other conditions as possibilities. Enchondroma is far more rare than intratracheal goiter. A mistake might possibly be made with a sarcoma, as it has, too, a broad, large basis and smooth surface, but the sarcoma grows very much more rapidly, and thus causes more intense dyspneic symptoms than the intratracheal goiter.

The origin of such tumors must be referred to embryonic residues included in the tracheal walls at the time of their development. In one instance, however, Paltauf showed microscopically that the intratracheal goiter in his case undoubtedly took its origin from a goiter developed in the isthmus of the thyroid gland, and that this had penetrated through the tracheal walls.

## CHAPTER XI.

### CONGENITAL GOITER AND GOITER IN CHILDREN.

#### CONGENITAL GOITER.

IF systematic examination of the neck of all newborn were made, certainly many more congenital goiters would be detected than actually are. Congenital goiter was described for the first time by Fodéré in 1796. This author was already impressed by the relation which existed between congenital and parental goiters. Hausleutner in 1810, Martin in 1840, von Ammon in 1842, Pflug in 1875, devoted a good deal of study to the question of congenital goiter and its relation to parental goiters but it is to Virchow and Demme that we owe the most careful study on this subject. Reviewing 642 cases of goiter, Demme found 37 congenital goiters; out of 2292 goitrous patients Diethelin saw 25 congenital goiters; out of 1996 goiters Richard found 43 cases of congenital goiter; and in 1909 Thevenot reported 133 cases of congenital goiter taken from the literature and from his own personal experience.

*Vascular and parenchymatous goiters* are the two most frequent varieties seen in the congenital form of goiter. *Colloid goiter* is very much less frequent. *Cystic goiter* is rare, but when present may attain enormous volume, as in Hecker's case reported in 1868, where the tumor was so enormous that it prevented the normal course of labor. Adelman and Hubbauer saw a congenital cystic goiter whose dimensions were  $1\frac{1}{2}$  times the size of the head of the newborn. Every once in a while it has been found that a congenital goiter had undergone *sarcomatous* degeneration. Many of the congenital goiters reported in literature as being of very large size were, as a rule, *teratomata*. Such large tumors are not seldom associated with other pathological conditions resulting from malformations or retarded development as hare-lip, situs inversus, etc.

The etiology of congenital goiter is the same as that of ordinary goiter. In the *vascular form*, however, the mechanical influences during labor and delivery, such as hyperextension of the head in face presentation, persistent occiput posterior positions, pressure on the fetus from uterine contractions, and prolonged labor and deliveries, intervene to a great extent as adjuvant etiological factors by increasing the congestion of the thyroid gland. On the other hand, congenital goiters have a great obstetrical interest. Situated between the chin and the sternum, they prevent flexion of the head during the passage of the fetus through



the pelvic route and hence cause face presentation. Sometimes, especially in shoulder or buttock presentations, the umbilical cord winds around the neck, thus increasing the congestion of the goiter. Finally, these congestive conditions are apt to occur during normal labor in conjunction with all pelvic deformities.

*Parenchymatous goiter* is, more strictly speaking, the true form of congenital goiter. The influence of heredity, especially on the mother's side, cannot be denied. Out of 53 congenital goiters Demme found that in 37 the parents had goiter, while in 23 cases the mothers alone were goitrous. Out of 43 cases Richard found 22 in which the mother had goiter, but in 1 only did he find goiter in both parents. In the 7 cases which I have seen and in the 9 cases reported by Rübsamman in each case the mothers had goiter. Furthermore, congenital goiter is far more prevalent in regions where goiter is endemic, but this is no longer surprising as soon as we admit that the causes which produce it are the same as the ones which produce endemic goiter. Syphilis or tuberculosis cannot be regarded as playing any part in the etiology of congenital goiter. Commandeur seems to think that congenital goiter is not found in primiparæ, as the 5 cases reported by him occurred in multiparæ. This statement, however, has not been confirmed.

Histologically the congenital goiter does not differ materially from the forms seen in adults except that its vascularization may be more intensely developed. Its volume is, of course, variable, but seldom exceeds the size of an egg. As a rule congenital goiter is entirely cervical; in some instances, however, it has been found intrathoracic. Congenital goiter may affect the *circular form* (Figs. 48 and 49); in that case it is most dangerous, as it may cause fatal spells of suffocation.

**Symptoms.**—Every congenital goiter does not necessarily produce symptoms. Many of these goiters remain *latent* and subside rapidly with or without treatment. In other instances, however, they grow and finally attain a large size. These goiters, as a rule, are not the dangerous ones, because everybody is aware of their presence, and since their symptoms are not alarming there is plenty of time to apply medical treatment, which, as a rule, is thoroughly successful. To be sure, they may disturb the little patient by their volume, and they may cause dyspnea and dysphagia; in the latter case the baby will refuse to nurse. In other more benign forms of congenital goiter, interference with respiration is only moderate and causes what is known as the *asthma neonatorum*. These cases, however, properly handled can be satisfactorily managed.

This is not true of the *fulminating forms* of congenital goiter. Oftentimes in that form of goiter the little child is born dead; if not, the accidents develop rapidly; cyanosis is intense; dyspnea is quite marked;

stridor with supra- and infrasternal tirage is present; the mouth and trachea are filled with mucus; the voice is hoarse; the wailing is weak, the cry rasping and shrill; the eyes are protruding, and death soon follows.

**Treatment of Congenital Goiter.**—To a certain extent the treatment of congenital goiter may be prophylactic. For instance, if to a goitrous woman who is known to have already borne goitrous children, thyroid extract or iodine is administered with caution during her pregnancy, the development of congenital goiter may be prevented.

When the swelling is mostly of congestive nature it soon retrocedes spontaneously; at any rate, ice applied over the region of the thyroid will be beneficial. When, however, the enlargement is mostly of parenchymatous nature, and when the symptoms are not too alarming, medical treatment should be started at once. The following iodine ointment is very effective and easily used:

Kal. iodat. . . . .	5.0 grammes.
Aq. dest. . . . .	10.0 “
Lanolin . . . . .	30.0 “
Vaseline . . . . .	70.0 “

The number of cases which I have seen, and which were so treated, responded beautifully to the treatment. It goes without saying that medical treatment will have no effect upon a cystic goiter.

When the child is born in a state of apparent death all the known means for resuscitating a baby should be employed. Warm baths for the lower half of the body and ice-water on the cervical region may be beneficial, while, as in one instance, the forward pulling of the lower jaw may put a stop to suffocation. Sometimes by grasping the thyroid tumor between the fingers and pulling it upward and forward, one may be able to bring back respiration. In that case pressure is due to incarceration of the goiter at the superior opening of the thorax. If this maneuver has succeeded the little patient may do better if he is kept lying flat on his back with a pillow under his shoulders and the head in hyperextension.

If, however, everything has failed, one should no longer hesitate. A transverse incision should be made over the tumor, and the goiter liberated and resected, unilaterally or bilaterally, as the case may be. If hyperplasia involves the isthmus more than the remainder of the gland, *isthmectomy* may be all that is necessary. If at the same time thymus hyperplasia is present, *thymectomy* must be done quickly.

It should always be borne in mind that the operation is in itself dangerous, as the little patients do not stand shock or hemorrhage. Yet there is nothing else to be done. The mortality in the few cases

that have been reported varies from 6 to 8 per cent. *Tracheotomy* is more dangerous than thyroidectomy, and, as a rule, fatal on account of the bronchopneumonia which follows. Furthermore, if we remember that in such conditions the trachea is covered by an enlarged, congested isthmus, extending from the larynx to the sternum, and through which one will have to go, and if we remember that below there are the thymus and the innominates, and that in children the windpipe is small, soft and easily eludes the knife, and if, finally, we remember that the operation must be done quickly, since the child is dying, then anyone will easily understand that tracheotomy under such conditions is difficult.

### GOITER IN CHILDREN.

Goiter in children is not at all rare, especially in regions or countries where goiter is endemic. As in adults, so in children, all varieties of goiter are found; the parenchymatous form, however, is more frequently seen than any other. Goiter may be localized to one lobe only or it may involve the entire gland. When nodular the goiter originates nine times out of ten in the right inferior pole. The nodules may be unique or multiple. The goiter may even be intrathoracic.

Simple goiter in children must not be considered as a mere incident. It is often accompanied by a constitutional syndrome showing a general physical depreciation of the little patient. As a rule these children are below the standard of health and development; they look frail and become fatigued easily. So far as treatment is concerned the same rules apply as those for any goiter seen in adults.

## CHAPTER XII.

### SIMPLE GOITER AND PREGNANCY.

DURING *pregnancy* the thyroid gland undergoes nearly always an increase in volume which remains more or less marked all through the puerperal period. Generally speaking, during this stage the thyroid is not only larger but contains more iodine and is more active physiologically. According to Seitz, this increase in volume occurs in 65 to 90 per cent of all cases of pregnancy. Out of 718 pregnant women seen by Rübsamman, 89.5 per cent of the cases showed a glandular enlargement. According to Lange, thyroid hyperplasia in pregnant women was found in 108 out of 133 cases, and when goiter existed previously it always increased in volume during pregnancy. Ripmann found that 50 per cent of pregnant women show a slightly enlarged thyroid during pregnancy. In his observations the maximum of enlargement attains during the fifth to sixth month. Von Graaf examined 654 pregnant women during the second half of their pregnancy; 48.7 per cent. of them showed a thyroid enlargement. The same author, examining 256 pregnant Viennese women, found that 44 per cent of them had goiter. Of course many of these women had had goiter prior to their pregnancy. This, however, does not disprove anything, since he then found that 38.5 per cent of these goitrous women showed a marked increase in the volume of their goiters during pregnancy and delivery. According to Freund and Lange, hyperplasia takes place sooner in multiparæ than in primiparæ; it appears in the fifth month in the former and in the sixth month in the latter. It begins to retrocede a few hours after delivery and keeps on decreasing in size for weeks after. The thyroid, however, usually does not return to its normal size. *Lactation* seems to be devoid of any influence over the volume of the thyroid.

The same seems to be true for animals. Halsted reported that partially thyroidectomized dogs showed evidence of hyperthyroidism as the time of parturition approached, but that the condition disappeared soon after delivery. The pups born of these dogs showed thyroids many times the normal size. Carlson found that the thyroids of pups whose mothers had non-toxic colloid goiter were identical with those of pups born of mothers with normal thyroids. On the other hand, pups from mothers with active thyroid hyperplasia had thyroids larger than normal in direct proportion to the degree of hyperplasia in the mother. The same



was true for kittens. Carlson further remarks that although these observations were made in a region where goiter was endemic among dogs, not a single puppy was born with enlargement of the thyroid unless the mother had goiter.

The increase in volume is due to hypertrophy and hyperplasia of the parenchymatous elements; colloid and cystic nodules, when present, are only slightly involved. According to Seitz, the increase in volume is due to the action of placental products upon the thyroid. This glandular hyperplasia appears to be intended to destroy the products of auto-intoxication and changes in the serum caused by pregnancy, and it seems that women who do not show any hyperplasia of the thyroid are very apt to have albuminuria and eclampsia afterward. That the latter part of the supposition is not simply based on coincidence was shown by Lange. Indeed, if in non-pregnant cats one-fifth of the thyroid is removed, no ill effects whatever are observed, but if the cats are pregnant the same operation causes at once albuminuria and nephritis. Thyroid opotherapy undertaken in such animals causes the symptoms to retrocede at once. Nicholson obtained the same results; the treatment with thyroid extract of four pregnant women with albuminuria and eclampsia gave very good results. Seitz, Döderlein and others believe, however, that eclampsia is of parathyroid origin and claim to have obtained good results with parathyroid feeding. Whatever the cause may be, it would not be out of reason to admit that the thyroid hyperplasia in pregnancy is a physiological process, most likely intended to deliver the organism of waste products taking their origin in the mother and in the child. Perhaps, too, this hyperplasia is intended to counterbalance the temporarily lost function of the ovary.

In the majority of cases during labor, and especially during delivery, the goiter increases materially in size. Sometimes it acquires such dimensions that bursting of the neck seems to be imminent. Dyspnea and cyanosis are very marked. It is seldom, however, that the dyspneic symptoms become such as to necessitate surgical intervention. During labor and delivery pains, on account of the pressure from the goiter, the carotid pulse disappears, as shown by taking the pulse at the temporal artery. Guyon considers this phenomenon as an attempt of nature to regulate the cerebral circulation. In goiters of long standing the goiter-heart is always present and must be regarded as a bad complication. In other conditions tachycardia may become a very troublesome and alarming symptom.

**Treatment.**—In all pregnant women the condition of the thyroid should receive careful attention. If this gland is found manifestly enlarged or altered, and if evidence of thyroid insufficiency is found, the active principle of the gland in some available form should be admin-

istered. On that point everybody agrees. *Small doses* should be given, and may be continued for several weeks or months.

As it has even been found that thyroid opotherapy started in the early period of pregnancy prevents thyroid hyperplasia, and furthermore, as it has been shown experimentally that it prevents albuminuria and nephritis in pregnant thyroidectomized cats, it might be worth while to undertake a series of observations in order to find out if it would not always be advisable to feed pregnant women with thyroid extract, in order, possibly, to prevent some of the dreaded complications of pregnancy, as albuminuria, eclampsia, etc.

In every case of pregnancy complicated with goiter, be it simple or thyrotoxic, or both together, the wishes of the parents regarding the life of the child should always be carefully ascertained, and the situation explained to them. Where children have been lost previously, and the parents are desirous of offspring, all possible means should be used to continue the pregnancy without, of course, undue risk to the mother. As soon, however, as pregnancy is terminated the physician or obstetrician should consider it one of his first duties to have the patient seek surgical advice and treatment for her thyroid condition.

When pregnancy complicated with simple goiter only has reached an advanced stage no one should become unduly alarmed; the course of the pregnancy should be allowed to go on, and in the great majority of cases everything will terminate to the entire satisfaction of the patient as well as of the attending physician, even if during labor dyspnea and cyanosis seem to threaten at first to become alarming. If, however, on account of that goiter the patient has previously lost a child, and if the symptoms have been such as to endanger the life of the mother, *elective Cesarean section before labor* should be selected.

In cases in which, before labor, the dyspneic symptoms are marked, and when there is congestion of the cervical region with "caput medusæ" highly developed, it is logical to assume that dyspnea will be greatly increased during labor. In such conditions, elective Cesarean section can be made before the labor pains have started. If labor and dilatation are already far advanced, *pituitrin*, judiciously administered, may greatly accelerate labor and shorten its duration. If dilatation is more or less complete, forceps may be resorted to. If dilatation is not far enough advanced, but engagement is well started, a vaginal Cesarean section may save both mother and child. As in these cases the sole object of surgical intervention is "to do everything quickly," the induction of labor with elastic bags is, of course, to be rejected, as it is too slow and too uncertain a process, and adds to the mother's nervousness, and, furthermore, exposes her to rupture of the uterus in delivering a child through a partially dilated cervix.

*Thyroidectomy* in such conditions should be undertaken only as a necessity, as the operation is rendered extremely difficult by the enormous active and passive congestion of the entire cervical region; furthermore, the thyroid during pregnancy is in a state of compensatory hypertrophy, consequently it is difficult to judge how much gland should be removed and how much should be left. Thyroidectomy will be a much safer process after the obstetrical period is over.

*Tracheotomy* must be considered only as a life-saving device.

In all these cases the administration of an anesthetic is a very serious matter, and should be given the greatest care and attention, for it may prove disastrous. When possible, surgical intervention should be done under local anesthesia.

## CHAPTER XIII.

### CLINICAL ASPECT OF MALIGNANT GOITERS.

IN 90 per cent of the cases, malignant goiter develops in an already preëxisting goiter; consequently it is more frequently found in regions where goiter is endemic. A malignant tumor developing in a normal thyroid is rare; it is nearly always a tumor of connective-tissue origin, as sarcoma, endothelioma, etc.

Malignant degeneration of goiter occurs mostly between the ages of forty and sixty years. To be sure, cancerous goiters have been found in younger people, even in children ten to twelve years old, but these cases are certainly not common. If we glance over Schmidt's, von Straaten's, Carranza's and Carrel's statistics we find that:

- 24 occurred from 20 to 30 years of age = 5 per cent of all malignant cases;
- 91 occurred from 30 to 40 years of age = 19 per cent of all malignant cases;
- 219 occurred from 40 to 60 years of age = 44 per cent of all malignant cases;
- 76 occurred after 60 years of age = 16 per cent of all malignant cases.

Sarcoma is more frequently found in young people, cancer in old ones. Malignant goiter is more frequently found in women than in men, and occurs mostly at the menopause, hence the *absolute necessity of removing any goiter which begins to grow at that time of life*. Infectious diseases seem to have a certain etiological influence on the development of malignant tumors of the thyroid. It is not so infrequent, for instance, to find that malignant degeneration follows an acute spell of grippe.

**Relations to Surrounding Structures.**—In advanced malignant goiters the skin is infiltrated, swollen, adherent to the deep layers, and is sometimes of a livid red, while underneath the veins are dilated, even thrombosed. The diffuse malignant infiltration may extend to the neck, muscles and other cervical organs.

In the majority of cases the deformations of the larynx and trachea found in malignant goiter, as compression and deviation (Fig. 51), existed previously and were started by the goiter itself. To be sure, such deformations may have become more accentuated since the malignant degeneration of the goiter occurred, but they are not typical of malig-



nancy except in terminal stages. The only feature which is characteristic of malignancy is the *invasion* of the tracheal walls by the tumor; in advanced cases it may even perforate them. Of course this perforation is facilitated by the previously existing atrophy of the windpipe, due to the pressure from the goiter itself.

The esophagus, too, becomes involved by the malignant degeneration. It seldom becomes perforated by the tumor. Compression may

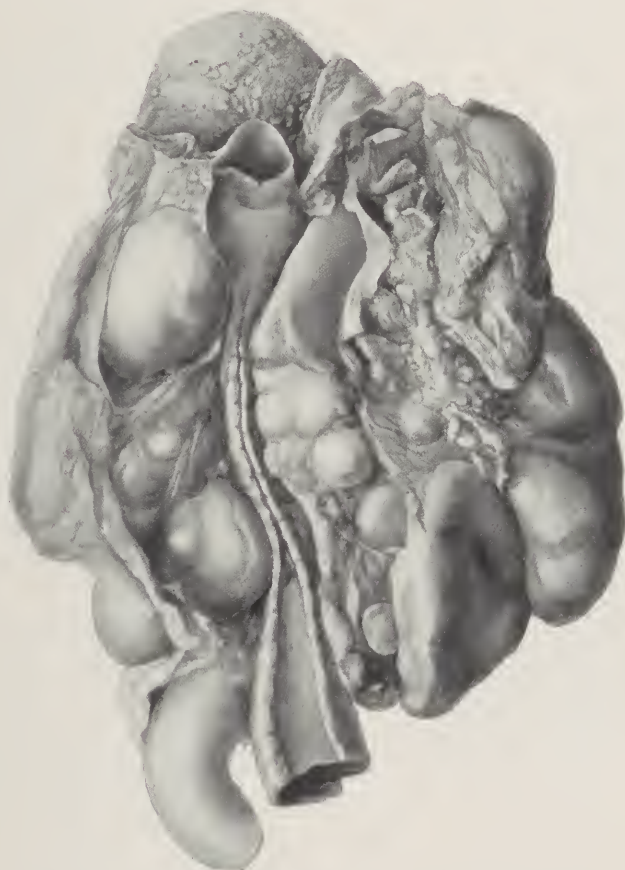


FIG. 51.—Pressure upon windpipe by a malignant goiter.

become so marked as to reduce considerably the size of the esophageal canal, hence dysphagia, and in the last stage, starvation.

The carotid sheath is usually found adherent to and compressed by the tumor. In advanced stages the malignant infiltration may involve the large vessels, erode them and cause a fatal hemorrhage, as in the cases reported by Oser, Lebert and Coulon. Such termination, however, is exceedingly rare. Less resistant than the arteries, the veins are fre-

quently invaded by the malignant tumor, and it is not infrequent to find them perforated and filled with cancerous masses. In one of my cases in which the cancer extended deeply downward into the mediastinal space, not only the imæ and jugular veins were thrombosed, but the carotid and the vagus were also involved, so that dissection was wholly impossible; veins, arteries and nerves had to be removed with the tumor. In another case I found the junction of the subclavian and jugular veins completely thrombosed and perforated by the tumor.

When malignancy has reached a certain stage, one or both inferior laryngeal nerves will nearly always be involved. The one on the left side is more often involved than the one on the right side. Both nerves may be involved at the same time. As told above, the *vagus* and *sympathetic* nerves may become so embedded in the tumor that their removal with the tumor is rendered necessary. This removal, however, does not materially influence the immediate postoperative prognosis, especially when resection is unilateral.

In cancer the involvement of the lymph nodes takes place early. The ones which are affected at first are the cervical, found along the carotid sheath; only later the mediastinal lymph glands become involved. As a rule malignant lymph nodes are small, round, hard, and form a chain along the carotid sheath. In a later period they grow and fuse together with the goiter itself. In some forms of malignancy the lymph nodes are large, soft, and remind one of a malignant lympho-adenoma. Involvement of the lymph nodes in some forms of malignancy may be totally absent.

**Course and Symptoms.**—The development of cancer may be *acute*, *subacute* or *latent*.

In the *acute* or *fulminating form* the development of the malignant tumor is extremely rapid. In three or four weeks it may reach such a development as to cause alarming symptoms of suffocation, since the trachea soon become caught in the diffuse, malignant infiltration. This form of malignant tumor occurs in young people, and is often mistaken for acute thyroiditis. It is often impossible to differentiate it clinically from the woody thyroiditis.

In the *latent form* the gland is hardly modified in form, size and consistency, but numerous metastases are found in the lungs, bones, etc. The thyroid origin of such metastases is usually discovered at autopsy or when the microscopic examination happens to be made from a lump removed by operation. This form of malignancy is rare.

Usually the development of malignant tumor follows the *subacute type*. It occurs in patients who previously had goiter, which may have been stationary for years. Some day, however, without any apparent cause, it begins to enlarge and to grow with comparative rapidity. It

soon interferes with respiration, the voice becomes rough, harsh and rapidly bitonal; deglutition is slightly difficult; shooting pains, especially toward the ear and along the cervical and brachial plexuses, are complained of. Little by little the limits of the goiter are less sharply outlined; the tumor becomes adherent to the muscles and other neighboring tissues (Fig. 52) and grows downward toward the mediastinal space. The goiter loses its previous softness and becomes *hard*. This is a symptom of great diagnostic value.

Gradually respiration becomes more difficult, a barking cough is frequent, and paroxysmal choking spells soon dominate the scene. These suffocating spells are always horrifying to witness. The face and neck are congested; the veins are distended; the eyes protrude and the patient makes desperate efforts to get his breath. His hands massage his neck, as if he were trying to remove the pressure. The choking spells succeed one another, and gradually the tracheostenosis grows tighter (Fig. 52); the tracheobronchial catarrh becomes more and more tenacious, and finally the end comes.

Percussion, auscultation, x-ray and laryngoscopic examination will give the same information as that of intrathoracic goiter.

On the anterior and superior portions of the thorax, when the malignant tumor has already progressed beyond a certain degree, there often is a collateral circulation, showing that the return flow of blood toward the heart is impaired. At the same time edema of that entire

region may be present, especially when the superior vena cava has been involved. Sometimes one may run across a cancer of the thyroid in which pulsations synchronous with the heart beat are distinctly perceived, so much so that one thinks of an aneurysm. This is due to the fact that the veins of the thyroid, being partially thrombosed, the return flow of blood is greatly impaired, and the impact of each new arterial arrival of blood is strongly transmitted through the congested and solid tumor. This form of cancer is called *aneurysmal cancer* (Figs. 53 and 54).

Dysphagia is among the first symptoms to betray the presence of cancer of the thyroid. Not infrequently this compression is accom-



FIG. 52.—Malignant goiter beyond operative stage.

panied by spasm of the esophageal musculature. In such conditions the swallowing of liquids, especially when cold, is as difficult as the deglutition of solid food.

Compression of the inferior laryngeal nerves, of the vagus and especially of the sympathetic, is frequently seen in malignant tumors of the thyroid. Symptoms caused by the injury of each one of these nerves have been studied when describing intrathoracic goiter, consequently there is no need to go over them again. Not infrequently patients complain of intense neuralgia in the arm, fingers and occipital region of the side corresponding to the tumor. These shooting pains are due to compression of the cervical and brachial plexuses.



FIG. 53

FIG. 54.

FIG. 53.—Malignant vascular goiter.

FIG. 54.—Two weeks after operation. Patient in good health eight years after operation.

Metastases must be carefully looked for; they may be found, or at least suspected, especially in the skeleton and lungs.

The blood formula in malignant tumors of the thyroid does not differ in any way from the one found in malignant tumors of other organs.

Symptoms of thyroid insufficiency in connection with malignant degeneration of the thyroid are not so frequent as one would expect. The reason for this is mostly because the entire gland is seldom involved. There remains nearly always enough gland to meet the physiological



requirements. And then, too, we know that malignant cells of the thyroid have not lost their physiological properties: they are still capable of normal function.

Symptoms of hyperthyroidism, as tachycardia, tremor, even exophthalmos, have been noticed quite frequently in connection with malignant tumors.

**Diagnosis.**—When no tumor is seen in the cervical region, diagnosis is difficult. In that case all the symptoms discussed in the chapter on Intrathoracic Goiter must be searched for. Diagnosis of a malignant intrathoracic accessory thyroid gland is seldom thought of. In differential diagnosis between tuberculous lymph nodes, malignant branchioma, cancerous lymph glands symptomatic of cancer of the esophagus, pharynx or even stomach, aneurysm of the aorta will have to be discussed. Too often, however, the true diagnosis becomes patent only at the operation.

Very much easier is the diagnosis of malignant degeneration of the thyroid gland when a tumor is present in the cervical region. In that case we have to deal with a patient who has had a goiter before, one which may not have given him any trouble thus far. Some day, however, without any apparent reason, the goiter begins to grow rapidly, and soon interferes with respiration and deglutition. Note, furthermore, that the patient is of middle age, that perhaps it is a woman undergoing menopause. Note, too, that the goiter has lost its softness and has become irregular in surface and peculiarly hard in consistency. This is enough to warrant a diagnosis of malignancy. If we add to this that the goiter has lost its sharp limits, that shooting pains are present, that the inferior laryngeal nerve has become involved, then the diagnosis of malignancy becomes more or less certain.

*Rapid increase in volume* of a goiter, which has remained inactive for a long time, and *changes in its consistency* are two excellent signs of malignant degeneration. What is true of the uterus is true, too, of the thyroid. If after menopause has taken place a uterus which has remained in a quiescent state for some time begins, without apparent reason, to bleed the chances are great that we have to deal with a malignant degeneration of that organ. The same is true of the thyroid. If a goiter, after a period of apparent inactivity, begins to grow, we must be on the lookout for every symptom tending to betray the malignancy of such a change.

Hemorrhages taking place at different intervals in a goiter might convey the impression that some malignant changes are taking place in that goiter, as there, too, we shall find a rapid increase in volume, hardness in consistency, slight diffuseness of its limits, shooting pains, slight temperature, etc., but further development will very soon show (in a few days) which one of the two conditions (hemorrhage or malignancy)

we have to deal with. Actinomycosis, tuberculosis and syphilis might cause the same, but these conditions are far more rare than malignant degeneration. The woody thyroiditis spoken of in the chapter on Strumitis might be mistaken for a malignant degeneration, but the mistake will be only beneficial to the patient, as an early operation may save his life.

Differential diagnosis between carcinoma and sarcoma of the thyroid is not always easy. Sarcoma, as a rule, grows more rapidly, reaches larger dimensions, is softer and has a smoother surface than carcinoma. In sarcoma the skin is less adherent and its limits are not quite as diffuse as in cancer.

**Treatment.**—There is only one treatment—*the knife*. All the other means are palliative measures only, and all are disappointing. Even the “knife” does not always fulfil its promises; we might even say that it seldom does. Let us hope, therefore, that the time is not far distant when biological chemistry will give us an easier and more effective measure than surgery, capable of curing this terrible disease.

Why is it that cancer of the thyroid as well as cancer of other organs has been for so long considered beyond surgical reach? Simply because all these cases are operated *too late*; hence disastrous immediate results; hence high mortality. We have in late years learned to know that cancer can be fought with some chances of success if it is operated early, namely, before the capsule of the gland has been invaded, before the veins have become thrombosed, and before the lymphatic glands have become involved. When the neoplasm is so encapsulated that it has not yet spread outside of its capsule, and consequently has not involved the neighboring tissues, the chances for a happy outcome are good; at least, we can hope that the patient will enjoy a comfortable and peaceful life for a year or two before any relapse occurs. Even that gain, though short—is it not worth our utmost efforts? Life is not so long after all that we should squander it lavishly.

We can properly say that the outcome of a cancer case lies within the power, not of the surgeon, but of the family physician. He is the one who sees these cases first; he is the one to treat them for months and months for simple goiter, before he realizes that something very serious is undermining his patient. He is the one who should consequently be educated to know such conditions, to differentiate them, and to make a very quick decision when once his doubts have been aroused. Every physician should always have in mind the possibility of a cancer in connection with any tumor. This possibility should haunt his brain in every case: he should be a “cancero-maniac.” The satisfied and dangerous optimism which is too often found, unfortunately too frequently finds its excuse in ignorance. It should be discarded and

replaced by an alarming pessimism. In this state of mind the physician will be able to catch the significance of any slight physical change in the tumor, the meaning of any apparently slight and insignificant symptom. Too often, indeed, these little prodromic symptoms are not paid enough attention, yet they exist. It is for us to train our senses to perceive them, and to utilize them for early diagnosis. Cancer, as a rule, does not appear like a thunderbolt in a clear sky, nor does a volcano emit its devastating lava without betraying its intentions by some previous uneasiness, some premonitory, earthly rumbling. To be sure, sometimes the early development of a cancer is insidious; in that case we are powerless. Then, too, the patient is too often guilty of an unpardonable negligence against which he should have been educated. Cancer is one of the few conditions in which it is not necessary to wait until diagnosis is certain. *Suspicion* is enough to warrant surgical intervention. When we have to deal with a patient of middle age whose goiter, without any apparent reason, begins to grow, to cause some shooting pains, to become hard, especially if this patient is a woman about the time of menopause, why wait until the entire cervical region has become as hard and rigid as a board, until the patient is choking to death—in other words, why wait until it is too late to operate? In a great many such cases an early operation, even when the diagnosis of cancer is still uncertain, will strike the neoplasm in its embryo, so to speak, and cure the patient. Even if an operation should be performed for a condition which, later on, proves not to be malignant, no harm will be done, as the patient will be relieved of his goiter, and may be saved from a future malignant degeneration of that tumor. Expectation and procrastination can only be fatal. They allow the newly starting neoplasm to reach a stage beyond which the words of Dante sound like a terrible condemnation: “*Lasciate ogni speranza voi ch’ entrate*” . . . . Lose all hope, you who enter. . . .

In operations for cancer of the thyroid *large incisions* must be used. The surgeon must be able to have a good view of the field and an easy access to the organs. There is no need to increase the difficulties of the operation by a narrow incision. Cosmetic results are of secondary importance.

If the neoplasm is still within the capsule and has not reached it, the operation will be a simple one; it will not offer more difficulty than the ordinary goiter. If, however, the malignant tumor has invaded the capsule and the neighboring tissues, the operation becomes extremely difficult. It may necessitate large sacrifices, as the resection of the internal jugular vein, the common carotid, the sympathetic and vagus nerves. The windpipe and esophagus may be so adherent as to necessitate their partial resection. The lymphatic glands and the tumor itself

may extend so deep behind the sternum as to render a radical operation impossible. In such conditions the immediate results are disastrous; the mortality is very high, and, according to the statistics of Brown-Potter, in 1900, the total mortality for thyroid operations for cancer varied between 72 and 85 per cent, depending on the stage of the development of the cancer. In such conditions not infrequently relapse of the tumor is noticed a few days after operation. In the most favorable cases, however, relapse occurs only two or three years after; exceptionally it may not appear at all, as in the cases of Roux and Kopp. In these, relapse had not occurred six years after an operation for a cancerous goiter in which a partial resection of the trachea had proved necessary. In 1900 Madelung reported 100 cases of malignant tumor of the thyroid; 59 times death followed the first month after operation; 39 times relapse occurred in the sixth month after operation while in the 2 remaining cases death occurred later. Two of my cases operated eight and nine years ago respectively are still free of any recurrence at the present time.

When the malignant degeneration involves both lobes, and when the necessity of a complete removal of the tumor subsists, the surgeon must not hesitate to sacrifice the entire gland regardless of the myxedematous consequences. Between the two evils, better choose the lesser one. Myxedema, if it does occur, can be easily taken care of by thyroid opotherapy. On the other hand, total thyroidectomy does not necessarily expose the patient to hypothyroidism, because accessory thyroid glands may be present; in that case they will furnish necessary thyroid secretion. Sometimes unsuspected metastases may be present; we know that such metastases are physiologically active, as illustrated by the well-known case of von Eiselsberg's.

Concomitant unilateral resection of the internal jugular, of the common carotid, of the sympathetic and vagus nerves with the tumor seems to be without importance so far as the postoperative course is concerned.

When the malignant degeneration has spread throughout the entire cervical region, and when the cervical organs have become embedded in a hard, diffuse, cancerous mass, no relief should be expected from surgery. The patient has to be more or less abandoned to his fate; at the most, relief may be sought through some palliative treatment. Among the most important of these palliative forms of treatment are *x-ray*, *radium* and *tracheotomy*.

Tracheotomy has proved extremely disappointing, so much so, that there are surgeons who prefer to let their patients die their own death. Such views are to a certain extent warranted, because tracheotomy in such conditions is an extremely difficult operation. The veins are enlarged and dilated; the skin is infiltrated; the cancerous mass sur-



rounding the trachea is thick, hard and non-elastic; the trachea itself is compressed, displaced, invaded by the tumor and rendered hardly recognizable (Fig. 52). Add to this that the patient is choking, that the operation must be done quickly without anesthesia, one will then understand why a surgeon might hesitate before attempting tracheotomy. Such difficulties, however, should certainly never deter a surgeon worthy of the name, if the results expected from such an intervention are thought likely to be satisfactory. But as said before, results are very disappointing. A great many patients die during the operation, a great many others die a few hours after, and many of those who survive, die a few days after, either because compression of the windpipe takes place low in the thorax, or because bronchitis or bronchopneumonia follows. Personally, I feel that if there is any chance to alleviate suffering, even temporarily, it is the duty of the surgeon to do so.

When *dysphagia* is very marked, feeding of the patient must be done with an esophageal cannula. Gastrostomy may become necessary.

### HYPOTHYROIDISM—MYXEDEMA.

**Synonyms.**—Cachexia pachydermia; Cachexia Thyroidea; Cachexia Thyreopriva, or Strumipriva.

In 1875 William Gull reported to the Clinical Society of London 5 cases of a disease characterized by a swelling of the skin, and a more or less complete apathy of the patient. The title of his paper was, "A Cretinoid State Supervening in Adult Life in Woman." (*Clinical Society Transactions*, Vol. 7.)

William Ord, in 1877, published 6 other new cases which he called myxedema on account of the edematous infiltration of the skin. Charcot, in 1879, reported other cases and called the disease "cachexie pachydermique." All the cases reported up to this time were found in women only.

Savage, in 1880, was the first to report a case of myxedema in the male. In the same year Madden called attention to the fact that in myxedema an atrophy of the thyroid gland was constantly present, but he did not see any etiological relation between these two conditions. He thought that atrophy was due to a vasoconstriction of the gland itself.

At about the same time Kocher, of Berne, and Reverdin, of Geneva, called attention to the results supervening after complete removal of the thyroid gland. Kocher gave to the clinical syndrome resulting from complete thyroidectomy the name of *Cachexia Strumipriva*; Reverdin called it *Operative Myxedema*.

**The Kocher-Reverdin Controversy.**—The publications of Kocher and Reverdin, appearing so nearly at the same time, have given rise to a long discussion as to whom the priority of the discovery really belongs. As the subject, so far as I know, has never been threshed out in English medical literature, and as it seems only just to give to each the credit to which he is entitled, I think it will be of interest to go to the bottom of this controversy. The medical public shall be the judge. Here are the facts:

1. In 1874, Kocher published a case in which after total extirpation of the thyroid, psychic and physical disturbances followed. In reporting the case in his "Pathologie et Therapeutique du Goitre," published in the *Deutsche Zeitschrift für Chirurgie*, Kocher said, "The future will show if relations exist between total extirpation of the goiter and the subsequent status of the patient, and what their nature will be."

2. On the 7th of September, 1882, while going to Geneva to attend the Congress of Hygiene, Kocher happened to meet Jacques L. Reverdin. Their conversation naturally drifted to surgical matters, and among them goiter surgery. When asked by Reverdin if he had noticed anything out of the ordinary after his goiter operations, Kocher said that he had seen one of his patients sink into a marasmic condition similar to cretinism, and that he was endeavoring to find the cause of such condition, as it might prove of great importance so far as surgery of goiter was concerned.

3. *Six days after this conversation* Reverdin made a short communication to the Medical Society of Geneva which I shall transcribe *in extenso*: Out of 14 operations for goiter there were 3 deaths, one from pneumonia, one from nervous symptoms, and the third, a malignant goiter, from suffocation. In patients who recovered, Reverdin noticed two or three months after the operation, weakness, paleness, and anemia; two of them showed an edema of the face and hands without albuminuria. In one patient the pupils were contracted; this patient had a dejected appearance, and his face became similar to that of a cretin. In the majority of patients this condition took a long time before disappearing, and in three of them this condition was still present after one year. Reverdin mentioned the fact that nobody had described such a condition before, but that Kocher a few days ago had told him that he had observed one similar case. "*Is this condition,*" asked Reverdin, "*due to traumatism of the sympathetic nerve, or to disturbances of the thyroid gland in its hematopoietic function?*" On account of such results Reverdin states that he has modified his technic. He used to perform total thyroidectomy when this was possible; now he saves a portion of the capsule of the gland. In one case where one lobe only of the thyroid had been removed, no secondary symptoms followed.

4. On the 4th of April, 1883, Kocher reported the results of 101 operations for goiter at the Surgical Congress of Berlin. In this communication Kocher gave a masterly description of a condition which he called *cachexia thyreopriva*. This description, based on about 30 cases of *cachexia thyreopriva*, was so completely and so clinically true that nothing of importance has been added to it since. Not only did Kocher give a full clinical description of that condition, but he also went a step farther and recognized, as an etiological factor of the disease, total thyroidectomy, and that physical as well as psychic disturbances seen in patients were due to a lack of thyroid function. With his marvelous and exquisite clinical sense, he claimed that there was a direct relation between thyroid insufficiency, cretinism and idiocy.

5. On the 15th of April, 1883, namely, 11 days after Kocher's paper at the Surgical Congress of Berlin, Reverdin, in the *Revue Médicale de la Suisse Romande*, began the publication of an article which was continued in the same journal on the 15th of May, 1883, and again on the 15th of June, 1883. These publications have since been united in one fascicule with the date, "April 15th, 1883," on the cover. This fact might mislead the judgment of the reader who is not aware of the combination of articles appearing in three different successive months and given the date of the first article. I shall summarize these three articles.

6. In the first portion of the article in the *Revue Médicale* of the 15th of April, 1883, his first article, Reverdin discusses the etiology and symptomatology of goiter and their relations to the neighboring tissues. Then follows the report of 9 operations for goiter. In Case 8, a few months after total thyroidectomy, this eminent surgeon noticed an edema of the face and hands, loss of strength, and dejected appearance. The other cases in which total thyroidectomy had been performed, and which survived, were all reported as being in *excellent condition*. No other reference to myxedema was made.

7. In the *Revue Médicale de la Suisse Romande* of the 15th of May, 1883, his second article, Reverdin adds the report of 13 other cases, making 22 in all, of goiter operations. In the fourteenth case, which had undergone total thyroidectomy, Reverdin was told by the family that the patient had lost strength and had swollen face and hands. As Reverdin saw this patient only from afar on the street, he could not control the truth of such statements. However, in April, 1883, when revising his cases, Reverdin did see him, and then the patient had completely regained his health. In Case 16, soon after total thyroidectomy, *tetany* occurred, which Reverdin considered as a symptom of hysterical origin. (At the time the real significance of tetany was not known.) Some time after the operation the patient became afflicted with "troubles bizarres." He gave no other description of these symptoms.

Thus out of 22 operations, 17 were total extirpations; 2 deaths occurred; 3 cases showed some peculiar symptoms which we know now were of myxedematous origin; all the other cases were reported *in excellent condition*.

Summing up the results of his operations, Reverdin concluded the article of May 15, 1883, in the following manner: "Total extirpation of the thyroid in goiter presents great advantages. It prevents relapse; when the gland presents several nodules of colloid or cystic nature, if the larger ones only are removed, the other small nodules are bound to grow, hence relapse of goiter. Total extirpation becomes a necessity when a diffuse, parenchymatous degeneration involves the entire gland. In such conditions partial thyroidectomy is not practicable. When the entire gland is pathologically involved, and when the condition of the patient does not warrant total extirpation in one sitting, total extirpation of the gland must be made in two sittings. Another advantage of total extirpation is to leave a large, clean cavity which heals up more readily than the one left by partial thyroidectomy. In the latter condition mortification of the glandular tissues left prevents prompt healing. On the other hand, total extirpation is more dangerous than partial thyroidectomy because the inferior laryngeal nerves are more easily injured."

On page 273 of the same article of the 15th of May, 1883, when speaking of partial extirpation of the thyroid, Reverdin says, "Partial extirpation of the thyroid is not a method of choice, but a method of necessity." In Case 19 Reverdin decided to perform a partial thyroidectomy because of the condition of the patient and says: "One might be driven against his will to perform a partial thyroidectomy. In conclusion when it is possible, total extirpation is certainly better so far as relapse is concerned; however, there may be cases in which prudence may oblige the surgeon to choose partial thyroidectomy before or even during operation." The great advantage as seen by Reverdin in partial thyroidectomy is to diminish the chances of injury to the inferior laryngeal nerves. *No reference whatsoever to myxedema.*

8. In the *Revue Médicale de la Suisse Romande* of the 15th of June, 1883, his third article, Reverdin deals at length with the results of thyroidectomies, giving supplementary information of Cases 8, 10, 11 and 14, which are cases in which myxedematous symptoms occurred after total thyroidectomy. (Why was such supplementary information not given before with the report of the cases, if such cases were really intended at the time to serve as the clinical working material from which the description of operative myxedema was to be derived?) In the same article Reverdin admits having read the résumé of Kocher's communication to the Surgical Congress of Berlin on the 4th of April, 1883, and



then gives a splendid description of the condition which he calls *Operative Myxedema*. In that article he clearly establishes the analogy existing between spontaneous myxedema of the adult and that following total extirpation. On the other hand, contrary to his previous statements, made four weeks before in the *Revue* of the 15th of May, 1883, Reverdin concluded finally that a partial thyroidectomy should be performed whenever it is possible, *reserving total extirpation of the thyroid for cases in which it cannot be avoided*.

Such are the facts and such are the data in which these various events occurred. From them we can draw the following conclusions:

1. Already in 1874 Kocher had been impressed by the peculiar physical and psychic conditions shown by his completely thyroidectomized patient. He did not at the time, however, recognize their true nature and origin.

2. When Reverdin and Kocher met on the 7th of September, 1882, and exchanged privately their views on goiter surgery and especially on its remote consequences, we can assume from what both said that each one of these illustrious surgeons was becoming aware of the fact that a certain curious and peculiar condition developed after operations for goiter, but neither one *seemed at the time* to have recognized its true significance.

3. The only official document on which Reverdin can possibly base his claim to priority of the discovery of myxedema is the short communication which he made to the Medical Society of Geneva on the 13th of September, 1882, and which has been reviewed above *in extenso*. Since then all that Reverdin wrote on that subject was *posterior to what Kocher said on the 4th of April, 1883*, at the Surgical Congress of Berlin, and is consequently of no avail so far as priority is concerned.

4. In examining attentively Reverdin's report made at the Medical Society of Geneva on the 13th of September, 1882, and which has been transcribed above, we can draw the two following conclusions:

- (a) The few remarks made by Reverdin cannot possibly have the pretension of a description of the disease as he mentions only, "the edema of the hands and face without albuminuria," and in one case the "cretinoid appearance." Others had called attention to this condition a long time before him. Gull, for instance, in 1873, and William Ord, in 1877, who called that condition *myxedema*, and Charcot, in 1879, who created the denomination *pachydermic cachexia*.

- (b) He did not see clearly that thyroid insufficiency was the etiological factor of myxedema. He did not know whether the gland or the sympathetic system was to blame.

5. After his report of September 13, 1882, Reverdin continued,

nevertheless, to perform total extirpation of the thyroid. His last was performed on November 17, 1882, namely, over nine weeks after his communication to the Medical Society of Geneva. It is to be regretted that Reverdin did not give the reports of all his cases of thyroid operations up to the time of his publication on April 15, 1883, as Kocher did up to April 4, 1883. On the other hand, Kocher, too, performed a complete thyroidectomy on November 27, 1882, and another one, his last, on January 16, 1883. From these facts what logical conclusions can we draw? Simply that at that time neither one had realized the exact significance of the disturbances seen after total extirpation of the thyroid. Kocher discovered their real meaning only when in January, February, and March, 1883, he reviewed his thyroidectomized patients and saw the results. So far as Reverdin is concerned, if he had discovered the real significance of total thyroidectomy and its direct relation to myxedematous symptoms, he could never have written what he did in the *Revue Médicale de la Suisse Romande*, May 15, 1883, namely, that total extirpation offered great advantages, and that partial thyroidectomy was not yet a method of choice, but a method of necessity. (See above.) Yet four weeks after, on June 15, 1883, in the *Revue Médicale de la Suisse Romande*, Reverdin says just the opposite. In his judgment, partial thyroidectomy should be given the preference, and total extirpation of the thyroid should be practised only when for some reasons it becomes necessary. Why such a sudden change? There is only one possible explanation: Reverdin had just read Kocher's publication of April, 1883.

Out of Reverdin's 22 thyroidectomies, 3 cases, possibly 4, showed unmistakable myxedematous symptoms. All the other cases were reported in *excellent condition*. Without injustice it can be said that there is certainly a disproportion between this meager clinical material to work with, and the splendid clinical description of *operative myxedema* given by Reverdin on June 15, 1883.

When once Kocher became convinced that myxedema was the result of total extirpation, he remained consistent with his conclusions. He never practised complete thyroidectomy again, and never advocated it under any circumstances except in malignancy. He gave his masterly description of myxedema which holds true today, and finally drew up the rules which in thyroid surgery have been the guide of each succeeding school of surgeons ever since. To posterity the name of Kocher will always be intimately associated with the thyroid subject, and to him belongs the credit of having, so to speak, discovered myxedema and its true significance. It would be unfair, however, not to give Reverdin justice and honor, as he certainly did suspect a part of the truth independently, and perhaps would have seen it all had he not been antici-

pated by Kocher. At any rate, his work, coming so soon after the one of Kocher, gave Kocher's conclusions more strength, and was certainly of great help in convincing the surgical public of the dangers of total thyroidectomy.

**Etiological Relationship between the Various Forms of Hypothyroidism.**

—If we compare the different forms of hypothyroidism, we shall see that there is between them an undeniable relationship, and despite the fact that sometimes notable differences exist between them, their etiological origin is *one*, namely, a *diminished*, or a *suppressed thyroid function*. Consequently, these different forms of hypothyroidism are only varieties of the same disease.

Let us consider, for instance, *the surgical and experimental hypothyroidism*. In these forms the thyroid has been entirely removed. The results of this total thyroidectomy in human beings as well as in animals are the same: the metabolism is greatly disturbed; a myxedematous infiltration of the skin takes place; the nervous system is deeply affected, and the intelligence is considerably reduced. If thyroidectomy has been performed in young animals, the growth of the skeleton and the development of their central nervous system are affected. In short, we have a complete physical as well as psychic degradation of the individual.

In spontaneous *adult hypothyroidism*, too, the symptoms are so strikingly similar to the ones found in operative and experimental myxedema that it is impossible not to see between them a close relationship. Since the cause of operative and experimental hypothyroidism is the loss of the thyroid's function, the same etiology is found in spontaneous adult hypothyroidism; the differences between them are only differences of degree. In operative and experimental hypothyroidism, as the thyroid has been abruptly and completely surgically suppressed, the clinical symptoms are very much more acute and rapid, whereas in spontaneous adult myxedema where the thyroid has undergone a slow process of atrophy and degeneration, the symptoms are chronic and slow; ultimately, however, the results are the same, namely, a well-characterized hypothyroidism. Consequently, from an etiological point of view, operative and spontaneous adult hypothyroidism can be identified. The first one is caused by the sudden, the second, by the slow suppression of the thyroid function.

Suppose, now, that we go a step farther and consider the spontaneous *infantile myxedema*. At the first glance, between this form of myxedema and the adult one, the differences are great, since in infantile myxedema we have an arrest in the intellectual development, namely, *idiocy*, and an arrest of physical development, namely, *nanism*. These two symptoms give to infantile myxedema a physiognomy of its own which is not found in adult myxedema. Consequently, at a superficial survey, these two dis-



eases seem to be entirely different, yet if we go back to what we see in experimental and operative myxedema we shall see that the relationship between these different forms is a close one. Hoffmeister and von Eiselsberg, after performing complete thyroidectomy in newborn rabbits, sheep, and goats, observed, besides the symptoms of myxedema usually found in adults, an arrest of physical development characterized by *nanism* and an arrest of intellectual development characterized by *idiocy*. Complete thyroidectomies performed in young children between eight and ten years of age, as reported by Bruns, Kocher, and Combe, give the same results. Consequently, we must conclude that these different forms of myxedema recognize the same etiology, and that the differences which exist between them are only due to the fact that in children the loss of thyroid function occurred at a time when the physical and intellectual growth were in the making; hence, nanism and idiocy. The sooner after birth the loss of thyroid function takes place the more marked will be the thyroid insufficiency.

What about *endemic cretinism*? There, too, as we shall see later in the etiology of that disease, the condition is caused by thyroid insufficiency aggravated by a noxious condition of endemic origin, which most probably exerts its noxious influence on the thyroid and on the entire organism not only during fetal life, but also through generations, so that, hereditarily speaking, that thyroid gland is normally below par.

We may then conclude the *surgical, spontaneous adult, spontaneous infantile hypothyroidism* and *cretinism* have the same relationship between them; they are only degrees of the same disease. The good results obtained by thyroid opotherapy in those conditions corroborate these views. What is of importance is not so much the presence or absence of the thyroid but its *loss of function*, and especially the *period of development* at which the thyroid ceased to functionate.

**Nomenclature.**—The denomination “cachexia thyreopriva,” or “cachexia strumipriva,” given by Kocher, is a far better one than “myxedema,” as the latter evokes in the mind one symptom only, namely, the mucinoid infiltration of the skin. It was adopted at a time when nothing was known of the etiology of the disease, and when the condition of the skin was the most striking symptom attracting the attention of observers. Furthermore, we know that in myxedema mucinoid infiltration of the skin is not always present. Consequently, this denomination is, strictly speaking, defective, yet it has become so common in the medical literature and has acquired such a strong hold that it would be difficult to change it.

On the other hand, if the denomination “cachexia thyreopriva” stands on a solid etiological basis, it nevertheless does not fulfil all the requirements, as it applies only to those forms of myxedema where the



gland is absent. It does not apply to cases of functionally insufficient thyroid glands. Consequently, this denomination, too, is insufficient.

If one reads the medical literature on myxedema, one cannot but be astonished at the great number of synonyms invented to designate the same thing, as "cretinism," "idiocy," "idiocy with pachydermic cachexia," "cretinoid pachydermia," "cretinoid myxedema," "myxedematous dystrophia," "infantile myxedema," "myxedematous infantilism," "spontaneous infantile pachydermic cachexia," "atrophic cretinoid myxedema," "pachydermic cachexia," etc. To the reader who is not familiar with all these matters, these different denominations are most confusing. Each one of these denominations seeks to set forth the side which struck most forcibly the mind of the observer who invented it, but none of them stands on a solid physiological and etiological basis.

As we know today, that all these various and differently designated forms of diseases have a common origin, namely, *absence or insufficiency, or inefficiency* of the thyroid function, it seems to me that it would be much more rational, clear and simple to classify them as follows:

I. <i>Athyroidism.</i>	Surgical.	{ Or cachexia thyreopriva. Or cachexia strumipriva.
	Congenital.	

These denominations would apply to cases in which the thyroid has been surgically totally removed or is congenitally absent.

II. <i>Hypothyroidism.</i>	Surgical.	{ Infantile. Adult.
	Spontaneous.	
	Fruste.	{ Infantile. Adult.

These would apply to cases in which the thyroid gland, although partly or even entirely present, has become *functionally insufficient*, as after partial or total thyroidectomies, or where the thyroids are degenerated, etc.

III. <i>Cretinism.</i>	Endemic.
	Sporadic.

By *endemic cretinism* we understand the peculiar forms of cretinism found in connection with endemic goiter. By *sporadic cretinism* we mean that condition of cretinism which occurs in regions where goiter is not endemic.

## CHAPTER XIV.

### PATHOLOGY OF THE VARIOUS FORMS OF THYROID INSUFFICIENCY.

**Thyroid.**—For a long time the etiological relation between the condition described as myxedema and the thyroid was not recognized, but after the researches of Ord, Olive, Schiff, Kocher and Reverdin it became known that an absolutely *sine qua non* condition for the development of myxedema was a lesion of the thyroid. This is so true that the English Commission appointed in 1884 to study the etiology of myxedema concluded that the only lesion which was constantly found in that disease was thyroid atrophy. “Without lesions or absence of the thyroid, no myxedema,” says Kocher. Hypothyroidism is a result of hypofunction of the thyroid either because the gland is partially or totally absent or because it is degenerated. At any rate, in hypothyroidism the thyroid is never normal.

In some cases of congenital athyroidism, microscopic examination shows no vestiges of the gland whatsoever. In such cases we have to deal with a congenital defect. An inflammatory process which would have destroyed the thyroid alone is hardly probable. This is evidenced by the fact that no traces of inflammation are discovered, and by the fact that the parathyroids are found absolutely normal. Indeed, if we remember how closely the parathyroids are related to the thyroid, and if we were to suppose that athyroidism were due to an inflammatory process, then the small parathyroid bodies would no doubt show some sympathetic symptoms, either clinically or microscopically. Such, however, is not the case. The parathyroids are always found normal. This fact proves, furthermore, that the parathyroids embryologically develop independently of the thyroid gland and that their presence does not prevent hypothyroidism from taking place. In some cases, however, it seems reasonable to admit that some toxic infectious influences have brought about the condition of athyroidism.

In the great majority of cases of hypothyroidism, however, the thyroid is present. A mass of sclerotic connective tissue takes the place of what was the gland before; it is hard and of a yellowish color. The epithelium of the alveoli is degenerated, and a thick colloid is present. Von Eiselsberg found in counting the number of cells of the alveoli, that they were greatly reduced in number and size as compared to the cells

of normal folliculi. Langhans believes that the gland has undergone an interstitial inflammation with leukocyte infiltration and endarteritis. The process, in his judgment, resembles the one seen in cirrhosis of the liver. In Stilling's case the entire gland had undergone a fatty degeneration and was represented by a mass of fat; the thyroid arteries were not present. In certain conditions the connective-tissue degeneration of the gland is so thorough that scarcely any traces of that organ can be found. Such cases might be mistaken for congenital athyroidism. Most probably the cases reported by Maresch, McCollum and Fabian belong to that class. In cases regarded clinically as congenital athyroidism, the presence of alveoli in the connective tissue of the cervical region has been detected microscopically.

In many cases of hypothyroidism and cretinism the thyroid, instead of being absent or atrophied, is, on the contrary, enlarged, but degenerated. In cretinism we can say that in 25 per cent of the cases the thyroid is absent or atrophied, and in 75 per cent of the other cases the gland is enlarged and degenerated. Microscopically, the acini are poorly developed, the normal elements of the gland are reduced and atrophied, and an intense colloid degeneration has taken place. As a rule, besides the degenerated portion of the gland, other parts are present which appear to be entirely normal. H. Vogt claims that a number of cases of cretinism have been found in which the thyroid was absolutely normal, and Bircher, examining the thyroid glands of 16 cretins, found the majority of them mostly normal.

**Skin.**—The infiltration of the skin with a mucine-like substance is a feature which is bound to strike the attention of the observer. It is to this condition that the disease owes its name, *myxedema*. A marked hypertrophy of the connective tissue of the chorion is present while the sebaceous and sudoriparous glands are atrophied. The connective tissue has an embryonic character; its fibers are dissociated, forming spaces in which a substance very rich in mucine is present. This semifluid substance filling up the interstitial spaces gives the entire skin a translucent appearance. The question whether this substance is really mucine or not is not yet settled. According to Halliburton, the quantity of mucine is fifty times larger than normally. On the other hand, Prudden, in the majority of his cases, did not find mucine. Some authors seem to think that the infiltration of the skin is not of mucinoid origin, but that it is due to an ordinary edema localized in the most superficial layers of the skin, hence the reason why this edema does not pit on pressure. Microscopically, the connective fibers of the chorion have a gelatinous aspect and are swollen. The lymphatic spaces are enlarged, and the nuclei of the endothelial walls voluminous. The majority of authors consider this process as a return to the embryonic stage. How-

ever, Virchow does not share this view. He believes that instead of being *regressive*, this process is an *irritative* one, similar to the one seen in *phlegmasia alba dolens* and *elephantiasis*. It resembles a granulation tissue containing an increased number of fibers and nuclei, partly infiltrated with an amorphous liquid of more or less mucinoid appearance. Ewald considers myxedema as a trophic disturbance and a degeneration of adipose tissue.

**Osseous System.**—In congenital athyroidism and spontaneous infantile hypothyroidism one of the most striking pathological findings is the retarded growth of the osseous system. Periosteal, as well as endochondral ossification, is extremely retarded. The epiphyses remain thin and cartilaginous. Cases have been seen where ossification was not completed at the forty-fifth year. The marrow of the bones shows a considerable fatty degeneration. These disturbances are so constant that they may be considered as typical of congenital athyroidism, congenital hypothyroidism and cretinism. The perichondrium as compared to the normal one is very poorly supplied with bloodvessels; the osteoid tissues, too, are very poorly irrigated. In congenital athyroidism and spontaneous infantile hypothyroidism the bones remain so short that, after growth is supposed to be terminated, the patient is and remains a dwarf. The thickness of bones, however, is less affected than their length. That all these osseous disturbances are due to the fact that the centers of ossification do not appear in due time is easily demonstrated by the *x*-rays. In a ten-year-old child, for instance, no traces of ossification were found in the *capitulum ossis Hamatum*, when they should have been present normally between the fourth and sixth months after birth. Dieterle has given a synoptical chart showing when points of ossification appear normally in the various bones of the hand. It is as follows:

Age.	Ossification appears in	Body length.
Newborn	Shaft of the phalanges, metacarpi, radius and ulna . . . . .	50 cms.
4 months	Capitatum, Hamatum . . . . .	60 cms.
5 "		
6 "		
7 "		
8 "		
12 "	Epiphysis of the radius . . . . .	75 cms.
1 $\frac{1}{4}$ years		
1 $\frac{1}{2}$ "		
2 "		
2 $\frac{1}{2}$ "		
2 $\frac{3}{4}$ "	Basilar epiphysis of the proximal phalanges . . . . .	85 cms.
3 "	Basilar epiphysis of the terminal phalanges . . . . .	95 cms.
	Other basilar epiphyses . . . . .	100 cms.



Age.	Ossification appears in	Body length.
3½ years	Os lunatum . . . . .	
4 "		
5 "		
5½ "		
6 "	Multangulum majus and minus . . . . .	108 cms.
7 "	Os naviculare . . . . .	110 cms.
8 "	Distal epiphyses of the ulna . . . . .	117 cms.
9 "		130 cms.
10 "	Os pisiforme . . . . .	
11 "		
12 "		
13 "	Sesamoid, hamulus ossis hamati . . . . .	150 cms.
16-17 years	Disparition of epiphyseal lines of fingers and metacarpi . . . .	165 cms.
18 years	Disparition of all epiphyses . . . . .	
19 "		170 cms.
20 "		170-180 cms.

Of course the pathological disturbances in the skeleton depend upon the time of life in which the thyroid insufficiency began to manifest itself; the sooner after birth the hypofunction of the thyroid takes place the more marked will be the disturbances in the osseous system. The pathological changes will be found mostly developed in the bones which were still cartilaginous at the time the thyroid insufficiency started to develop. For that reason the fibrous bones of the cranium are the least affected; they continue to grow to a certain extent while the development of the other bones is arrested, hence a disproportion between the head and the skeleton, hence a macrocephalus on the body of the dwarf. The growth of the bones of the skull, however, is far from being normal; the large fontanelle remains open and synostosis of the cranial bones is considerably retarded. Kyphotic and scoliotic anomalies of the spinal column are quite frequent.

Some authors, as Bourneville and Hertoghe, have claimed that in congenital athyroidism and spontaneous infantile hypothyroidism, deformation and retarded ossification of the osseous system were due to *rickets*. But in rickets we have to deal with an osteoporosis and a deficient calcification, whereas, in athyroidism and hypothyroidism, simply with an arrest of ossification. In *rachitism* the epiphyseal lines, instead of being linear, as in thyroid insufficiency, are irregular, and have a "saw-tooth" outline; furthermore, in rickets the appearance of the points of ossification is not retarded as in hypothyroidism, but takes place in due time.

**Nervous System.**—Whitewell found in examining the brains of myxedematous patients that the nervous cells were irregular, their prolongations reduced in number and their nuclei not staining as readily as the normal ones; vacuolization was present and neuroglia was increased.

It seems that these pathological findings are not specific for hypothyroidism, inasmuch as they are also found in other pathological conditions. Nowhere in the central nervous system can alterations specific for hypothyroidism be found. Study of the brains of cretins has not been done sufficiently to enable us to draw practical conclusions from it. Their weight has been found to vary between 1000 and 1400 gms. Microscopically, nothing typical has been found.

**Vascular System.**—Von Eiselsberg found atheromatous degeneration of the bloodvessels of thyroidectomized goats. The same results have been found clinically since. Very advanced atheromatous conditions of the large bloodvessels have been reported frequently in very young myxedematous individuals. Even amyloid degeneration has been observed.

**Genital Apparatus.**—In congenital athyroidism, infantile hypothyroidism and cretinism the genital apparatus, as a rule, is not sufficiently developed; even if the cretin reaches an advanced age, the genital apparatus remains of the infantile type. Their genital capacity is negative: "Nemo dat quod non habet." These congenital disturbances are, of course, in proportion to the degree of thyroid insufficiency, and with the period of life in which such insufficiency has taken place. In hypothyroidism of milder degree the genital apparatus is better developed. Such individuals are even able to procreate, although ordinarily their offspring come into this world cretins, hydrocephalous or dead.

**Glands of Internal Secretion.**—The *hypophysis* in cretinism and hypothyroidism has been reported from various sources as being pathological. Normally, its weight varies between  $\frac{1}{2}$  and 1 gm., consequently all that is found above or below these figures may be considered as pathological. Rogowitsch and others found experimentally that the hypophysis after extirpation of the thyroid underwent hypertrophy. This was regarded by these authors as a vicarious function of the hypophysis toward the thyroid gland. Schönemann, however, did not confirm such views. In examining 112 hypophyses of goitrous individuals he found that the hypophysis was atrophied in direct proportion to the goitrous degeneration of the thyroid gland. On the other hand, Boyce and Beadles, Bourneville and Bricon, Pisenti and Viola, were Ponfick found that in cases of hypothyroidism the hypophysis was hypertrophied. The alterations found in the hypophysis involve the anterior lobe of the gland only. Abnormal connective-tissue development, fatty or colloid degeneration, necrosis and ischemia of the cells, diminution of their number, distention of the little gland by a plasmatic fluid, all these pathological conditions may be found at the same time, or separately. Chromophile cells seem to be decidedly increased in number, are enlarged, and remind one of the cells with colloid degeneration.

The *thymus* has up to this time not been paid much attention. In a few cases, however, it was found hypertrophied, as in Bayon's case. On the other hand, Pineles and Bernheim Kasser reported a hypoplasia of the thymus in cases of congenital athyroidism; in that case the thymus was microscopically free from lymphocytes and Hassal's corpuscles, whereas the connective tissue was highly developed. This might be considered as a counterbalance of what we find in Basedow's disease, where the thymus is hyperplastic.

Researches on *pancreas*, *suprarenal bodies*, and other glands of internal secretion have not yet been made.

**Surgical Athyroidism and Surgical Hypothyroidism.**—These conditions come on, as a rule, after total or almost total extirpation of the gland and may appear in a few weeks, months, or even a few years after thyroidectomy. Young people are much more markedly affected than old ones, and the pathological picture is more marked in cases of long standing than in those of more recent date. The clinical picture following total thyroidectomy differs according to the period of life in which the loss of thyroid function takes place.

**Symptoms.**—At first the patient feels weak and tired. The lassitude following slight physical exertion is extreme, as shown, for instance, by the patient of Reverdin's, who, although a great walker, could not, after having undergone total thyroidectomy, walk more than one or two miles without being completely exhausted. Pain and heaviness in the limbs, tremor of the extremities, a sensation of cold are the most usual complaints of such thyroidectomized patients. Their movements become slow and awkward; they lose their capacity for doing fine or precise work; they lose the coördination of their movements. If the patient is a barber he drops his scissors or razor unexpectedly; if a seamstress, she can no longer do fine needlework; if a cashier, he can no longer deal out money easily and quickly, etc. Naturally, this awkwardness reaches its maximum when the hands become edematous.

At the same time the intellectual power diminishes; the memory becomes weak; speech is difficult or slow; the patient becomes apathetic. At first, especially if it is a child, the patient may try to conceal his handicap as, for instance, the young girl spoken of by Kocher, who in school made desperate efforts to keep up the pace with her schoolmates. The patient, however, soon realizes that something is wrong with his intelligence, and becomes silent, shy, and self-contained.

When the disease is well established the face is large and swollen. The eyelids, especially the inferior ones, show a semitransparent saciform swelling, which, always to one's surprise, does not pit on pressure. As these edematous eyelids partially cover the line of vision the eyes look small and sunken. The nose is large; the lips thick, hanging, and

cyanotic; the ears are enlarged and thickened; the lines of the face being puffed, have lost their mobility and are without expression, and hence give an air of stupidity which recalls cretinism. The skin of the hands, feet, and of the body gradually becomes swollen. This edema is more pronounced in the morning, and differs from the edema of kidney and cardiac diseases by the fact that it does not pit on pressure. The skin is dry, shows a yellowish-white, dirty color, and scales easily; perspiration is more or less suppressed; the hair is scarce; the patient "looks old." The swelling of the skin extends to the mucous membranes; the tongue is thickened. The patient becomes anemic; the blood shows a diminution of red corpuscles, and a relative increase of leukocytes: this leukocytosis increases with the degree of the disease. The pulse is small and the heart, as a rule, shows no changes. The temperature is lowered, the circulation, and digestive functions become less active. Sensibility to pain and touch is diminished. In short, the mental as well as the physical processes are considerably reduced.

If total thyroidectomy has been performed in a young child, its growth stops and its intellectual faculties regress rapidly. This is very well illustrated by the case of Dr. Sick, who in 1867 performed a complete thyroidectomy in a ten-year-old child. This boy, who was extremely intelligent, gradually lost his mental and intellectual energy to such an extent that when seen by Bruns, eighteen years after, he had the appearance of a perfect cretin. He was incapable of rudimentary work, and could not answer the most elementary questions. His stature was the same as at the time of the operation; his head only seemed to have developed and was out of all proportion to the rest of the body. Kocher, Combe and others have reported similar experiences. If total thyroidectomy is performed in a later period of physical development, the symptoms of hypothyroidism will be less marked. These symptoms present their minimum when growth and sexual development are terminated. The condition then becomes harmless, *quoad vitam*; it affects only the patient's efficiency and often renders him incapable of attending to his business, thus forcing him to give it up, such as the barber who constantly dropped his scissors or razor; the seamstress who could not remember measures; the maid who dropped everything which she picked up, or the student who had become unable to remember the simplest facts of mathematics.

When hypothyroidism affects a severe form the patient dies either from the condition itself or from an intercurrent disease. In other instances after a more or less prolonged period of development, hypothyroidism may regress spontaneously, become less severe, and in a few instances may even disappear entirely. Indeed, it has been demonstrated in a great many cases by many authors that total extirpation of



the thyroid is not always followed by cachexia strumipriva. At first this seems not in harmony with the classical belief that the complete removal of the thyroid causes hypothyroidism. This inconsistency, however, is only apparent, for we know now that this failure to follow the rule is due to the fact that the gland has not been entirely removed, a small portion of it having been left, as the processus pyramidalis, for instance. It may also be due to the presence of accessory thyroid glands, which are, as we know, not uncommonly found in the cervical or mediastinal regions; as soon, however, as these accessory glands are removed, cachexia strumipriva follows. Cases of hypothyroidism have been known to develop after the removal of a lingual goiter.

More perplexing are the cases of "partial" thyroidectomy followed by a well-defined hypothyroidism. Why is it so? We must remember that certain individuals have just enough thyroid to meet the ordinary physiological demands. They are constantly verging on thyroid bankruptcy. Therefore it will be easily understood that the removal of a portion of that gland puts them at once in thyroid physiological inferiority. In other cases postmortem has shown that after partial thyroidectomy the remaining portion of the gland has become atrophied and invaded by the connective tissue to such an extent that the glandular elements have been partly destroyed: hence, again, producing functional insufficiency. It goes without saying that so far as thyroid insufficiency is concerned it does not matter what portion of the gland is removed; in ordinary conditions, if any part of either of the two lobes or isthmus, or if any accessory thyroid gland remains, hypothyroidism is not to be feared.

**Spontaneous Adult Hypothyroidism.** (Fig. 55).—This is eminently a chronic disease. It progresses slowly and it is only after years have elapsed that it reaches its maximum.

**Etiology.**—Excitement, traumatic lesions of the neck, numerous pregnancies, especially when accompanied with much loss of blood intrapartum, tuberculosis, alcoholism, and syphilis, have been thought to be the cause of spontaneous adult hypothyroidism. Most likely all these conditions should not be regarded as the *primum movens*. They have most probably supervened in conditions of hypothyroidism already existing, although latent. As said before, in certain patients as long as conditions remain normal the thyroid is barely physiologically sufficient; but as soon as it is overtaxed it becomes momentarily or permanently insufficient to the task: hence thyroid insufficiency.

Spontaneous adult hypothyroidism is often found in conjunction with goiter (Fig. 56). Among the most important causes of spontaneous adult hypothyroidism are acute infectious diseases. This etiological factor is being recognized more and more every day. We have seen in

the chapter on Strumitis and Thyroiditis that the thyroid does not remain indifferent in the presence of all infectious diseases, acute or even chronic. It reacts more or less intensively, a bacterial or a toxic thyroiditis setting in; in many instances, it may even reach suppuration. After the acute inflammatory stage is over, the process is by no means terminated. In many instances an insidious, treacherous, chronic inflammation remains, characterized by a diffuse production of connective tissue whose ultimate result is the destruction of the secreting epithelium of the gland, hence thyroid insufficiency. This influence of infectious disease is very well illustrated in one case reported lately by Achard: myxedema developed in a child ten years old some time after measles, and after forty-two years' duration of the disease the patient died.



FIG. 55.—Spontaneous adult hypothyroidism. The thyroid gland is barely palpable.



FIG. 56.—Spontaneous adult hypothyroidism in conjunction with colloid degeneration of the thyroid gland.

The postmortem showed no traces whatsoever of thyroid tissue. In many other instances, however, production of connective tissue seems to be of secondary importance. Impaired physiological activity of the thyroid cells themselves seems to be responsible for the hypothyroid symptoms.

Spontaneous adult hypothyroidism, although found everywhere, is far more frequent in regions where goiter is endemic, and in individuals whose thyroid is congenitally insufficient on account of their goitrous parentage. It is rare in the tropics, occurs frequently in cold climates, and is very common in certain countries, especially in France and Switzerland. It is less common in North America. Cases of spontaneous adult hypothyroidism have been reported among negroes.

It is more common in women than in men. Prudden, in 1888, found 145 cases—32 men and 113 women. Heinzheimer, in 1894, out of 150 cases, found 10 men and 117 women. (In 23 cases the sex of the patient was not given.) The predisposition of women to spontaneous adult hypothyroidism is due to frequent congestions and toxi-infectious disturbances of the thyroid during sexual life, such as menstruation, pregnancy, menopause. It is more common between the ages of thirty and fifty years.

**Symptoms.**—As the patient has reached his complete physical and mental development the symptoms found will correspond to the ones seen in operative myxedema of the adult; the skeleton is normal, and the disturbances of a psychic order are not so marked as in infantile hypothyroidism. The organs are not anatomically but only functionally disturbed.

The debut of the disease is insidious, slow, and progressive. Without apparent cause, more often during the convalescing period of an acute infectious disease, a progressive weakness, physical apathy, and an intellectual torpor combined with anemia are observed. The true significance of such conditions, as a rule, is not understood and the patient is treated for anemia. Under medical treatment and rest these conditions are improved or retrocede entirely, but after a few weeks or months they relapse again, and then, if not properly treated, follow their slow but progressive course, which may last ten, twenty or even forty years.

In the full development of the disease the face is swollen, the lips are thick and everted, especially the lower one, and the nose and mucous membrane of the nasopharynx are swollen, too. This swelling compels the patient to breathe with open mouth while sleeping, hence causing loud snoring. The tongue is thick, chin plump, and on account of the swelling of the eyelids the eyes seem to be smaller; the cheeks are flabby and the lines of the face have a remarkable immobility; this altogether gives the patient an air of stupidity. His forehead is often wrinkled and his eyebrows are elevated in order to raise the swollen lids above the line of vision. In opposition to what is seen in cardiac and renal diseases where edema obliterates the wrinkles of the face, in myxedema it exaggerates them. The skin is yellowish white, waxy, with a slight touch of pink on both malar regions.

The myxedematous infiltration is not evenly distributed over the body; there are places in which it is more prominent than in others, for instance, in the supraclavicular spaces, abdomen, neck, and thorax. Because of lack of perspiration the skin is dry and scales off easily. The sebaceous secretion is scarce and skin eruptions of different kinds are often present.

The hands and feet are thick and clumsy, the fingers have the shape of small, round sausages, and move with difficulty; hence the name "spade-hands" given by Gull. The patient does not use them with ease, hence, awkwardness. Feet and legs become round and thick, and have a pachydermic appearance. The hair and eyebrows are thin and brittle, while in the axillary and pubic regions the hair falls out.

The symptoms evidenced by the nervous system are very striking. They consist in a weakened memory, slow mental processes, diminution of the capacity of coördination, and diminished activity of the organs of sense and of the reflexes. The patient answers questions slowly and becomes irritable if pressed with them. Although he may usually be of a gentle disposition, he will at times show remarkable bursts of rage. Any mental or physical exertion is a burden to him; his speech is slow, but not stammering or monosyllabic. His slowness is due to a slow process of ideation. His voice is more or less husky on account of the edema of the laryngeal mucous membrane. The organs of special sense are quite often affected: hearing, sight, taste, and the sense of smell are diminished. Deafness, to a greater or lesser degree, is common, and is not only due to infiltration of the mucous membrane, but also seems to be of central origin. Tinnitus is quite frequent, and is the source of much complaint on the part of the patient. The sense of touch is reduced and the patient is sensitive to cold. This sensation of cold is not only purely subjective, but is also objective, as the central temperature of the body is lowered and varies between 95° and 97° F. The extremities, lips, and nose are cold and cyanotic; the circulation is slow and the pulse varies between 50 and 65. As a rule the heart shows no abnormality.

The red corpuscles may be slightly diminished, and the hemoglobin content reduced. But just as for Graves's disease, the most characteristic changes concern the white cells, so here, too, as shown by Kocher, we find leukopenia, hyperlymphocytosis, and hyperpolynucleosis. The coagulability of the blood, on the contrary, as shown by Kottmann, is reduced in hypothyroidism, whereas it is increased in hyperthyroidism. This is a point of very good differential diagnostic value. The urine is diminished and its specific gravity varies between 1000 and 1015. The nitrogenous exchanges are low. Menstruation when present may be profuse or scarce, but very often is suppressed. The patient complains quite often of rheumatic pains in the hands, feet, and back.

The clinical picture of spontaneous adult hypothyroidism is not always so complete; many cases have been described in which only a few of the above symptoms recorded as characteristic of hypothyroidism have been found. These cases are called *fruste*, *larvate* or *incomplete hypothyroidism*. They were described by Brissaud and Tiberge and called



by Hertoghe, *mild hypothyroidism*. They are more frequent than one would expect. We shall study them in another chapter.

In senility the thyroid gland becomes atrophic, undergoes a diffuse sclerosis which gradually tends to destroy the epithelial elements of the gland itself, hence hypothyroidism. According to Horsley, old age is only a form of mitigated hypothyroidism. He believes that the people that enjoy a green old age owe this happy condition to a thyroid which has remained normal. The points of resemblance between senility and a slight degree of hypothyroidism are more than one. The changes in the face, the falling out of the hair, the dryness of the skin, the production of adipose tissue, the diminution in the function of the nervous system, of the sensorial, intellectual, and genital spheres, all these symptoms found in advanced old age, according to Horsley, point toward a thyroid insufficiency of moderate degree. In both cases the nutritional exchanges are diminished; the pulse is slow; the temperature is low and a sensation of cold is present. "The only differences," says Ewald, "is that in old age there is a constant atrophy of the intestinal tract which is not present in hypothyroidism."

If these views are correct, thyroid opotherapy should be of great value in preventing old age, but I am afraid that this theory, although extremely interesting, is a sister to the Brown-Séquard theory, and we know that the promises of this have not been fulfilled. They who are dreaming the dream of Faust and Ponce de Leon, the dream of eternal youth, must still put their trust in something else than in the feeding of testicular or thyroid extract.

## CHAPTER XV.

### CONGENITAL ATHYROIDISM, SPONTANEOUS INFANTILE HYPOTHYROIDISM AND CRETINISM.

IN this class we shall include all these conditions which have been labelled at various times as "sporadic cretinism," "congenital or infantile myxedema," "idiocy," "pachydermic cachexia," "cretinoid pachydermy," "cretinoid idiocy," and "infantile myxidiocy."

In children thyroid insufficiency takes place at a period of their development when intelligence and growth are incessantly undergoing changes, consequently, hypothyroidism in children will differ from that of adults. *Nanism*, or arrest in the physical development, and *idiocy*, or arrest in the mental development, are the chief differential characteristics. Here, too, as in the previously described forms of thyroid insufficiency, all stages will be found.

If at birth the thyroid is totally absent, nanism, idiocy, and other hypothyroidism symptoms will reach the maximum of development. This is the *congenital* form of athyroidism. If thyroid insufficiency develops at a later period, when the body has already undergone a certain evolution, and when the intelligence has already awakened, nanism and idiocy will be less marked. The child will not be an *idiot* but only an *imbecile*. If thyroid insufficiency develops at a time when the physical and intellectual developments have already reached an advanced growth the symptoms will be less marked, nanism will be only sketched; the intellectual disturbances will be less noticeable, and then the little patient will not be called an idiot nor an imbecile but simply a *retarded child*. Finally, if the thyroid insufficiency is still of a milder degree the symptoms of thyroid insufficiency will be benign, too. Let us call this condition *fruste infantile hypothyroidism*.

**Etiology of Congenital Athyroidism and Spontaneous Infantile Hypothyroidism.**—In countries where cretinism is not endemic, cases of cretinism are found which resemble closely the endemic form, yet they do not acknowledge entirely the same causes. They are due solely to the absence of the thyroid or to its insufficiency. Exogenous influences from water and soil do not intervene as etiological factors. Such conditions are met with in congenital athyroidism and spontaneous infantile hypothyroidism.

*Congenital athyroidism* due to a complete absence of the thyroid must be regarded as a malformation; it is a congenital defect whose

cause is still very obscure. Probably, as in other forms of congenital malformations, something interfered with the normal development and arrangement of embryonic cells. This congenital thyreo-aplasia is not special to certain countries, has no relation whatsoever to endemic cretinism, and differs from the endemic hypothyroidism by the fact that there is no endemic goiter or cretinism in the ascendants.

In *spontaneous infantile hypothyroidism* (Fig. 57) the thyroid is always present; it may be either atrophied or even hypertrophied; the latter condition occurs very seldom. When present, however, hypertrophy is never very marked. The cause of this form of hypothyroidism may be dated back to infectious diseases of the mother during pregnancy. We know that the placenta is permeable to microörganisms, therefore it is logical to admit that it is that much the more easily permeable to their toxins which are liable to cause an acute toxic thyroiditis of the fetus *in utero*. Later, this thyroiditis takes a chronic form, the thyroid undergoes atrophy, hence a thyroid insufficiency after birth.

Tuberculosis and syphilis have been incriminated, too, as a causing factor of infantile thyroid atrophy. Alcoholism of the mother during pregnancy has been found, too, as a cause of thyroid insufficiency in the child. We know that it has been experimentally demonstrated that alcoholism has a damaging influence over the thyroid, consequently it is permissible to assume that in cases of severe alcoholism of the mother during pregnancy, alcoholic intoxication of the mother may damage the thyroid of the fetus *in utero*. Severe and prolonged congestions of the thyroid due to dystocia during delivery have in some instances been followed by thyroid insufficiency. Girls are more often affected than boys.

When hypothyroidism appears during the first years of infancy, after the child has been seemingly normal, the cause of such thyroid insufficiency may be found in the acute diseases which are the appanage of childhood, such as enteritis, whooping-cough, measles, pneumonia, etc.

**Cretinism.**—**Etiology.**—According to Kocher the name “cretin” comes from the French word “chrétien” (Christian), the intention being



FIG. 57.—Spontaneous infantile hypothyroidism, with some other polyglandular symptoms.

to convey the idea of innocence and simple-mindedness. Bayon thinks that the word "cretin" comes from the Rhaeto-Romanic word "cret," which means *cripple*, *cretin* or *dwarf*. Others think that it is derived from the word "creta," which means chalk, because of the color of the skin. The following anecdote related by St. Lager might confirm Kocher's idea, namely, that the word "cretin" comes from the French word "chrétien." "A mayor of a French village received one day a circular letter asking him to fill up an enclosed blank purporting to establish the number of disabled people of the town. After filling the columns concerning the blind, the lame, the hunchbacks, the lunatics, etc., the mayor stumbled upon the column 'cretins.' 'Cretins? What is that?' Everybody in the office was consulted, but nobody knew the meaning of the word cretin. Finally, the policeman was sent for and consulted. After thinking a while, 'By George,' said he, 'that is a typographical error. They ask you how many Christians (chrétiens) there are in your town.' The problem was solved. So the mayor wrote in the column of 'cretins,' 'We all are.'"

Cretinism is a peculiar clinical form of thyroid insufficiency, and belongs to the same pathological class as surgical, congenital, infantile, and adult hypothyroidism. Many of the symptoms of thyroid insufficiency seen in these latter conditions when compared with those seen in endemic cretinism show such a striking similarity that a parental relation between them cannot be denied. Although in every one of these conditions we find disturbances of the skin, of the osseous system, and of the genital and nervous apparatus, yet a closer examination shows that fundamental differences exist between cretinism and the other forms of thyroid insufficiency. In endemic cretinism, for instance, pathological changes of the skin are present, but they have not the same character as those seen in myxedema. Scholz says that the skin of the cretin cannot be even called "pseudomyxedematous." Bircher claims that in 60 per cent of his cases of cretinism, myxedema of the skin was not present. Osseous disturbances of the skeleton in endemic cretinism differ from those seen in congenital athyroidism. In the latter condition endochondral and periosteal ossification is considerably retarded; ossification in the epiphysis and synchondrosis takes place only very late in life; the fontanelles remain open for a considerable period of time, as seen in the postmortem of the "Pacha de Bicetre." In cretinism the retarded ossification is very much more irregular; only certain epiphyses and synostoses undergo normal ossification, whereas others do not. Sometimes we may see premature synostosis, hence disproportion between different parts of the skeleton.

One of the remarkable features of endemic cretinism is that the diminution of cerebral power is not always in proportion to the disturb-



ances seen in other systems of the organism. The course of the disease is different, too. In endemic cretinism, after a certain period of time, the disease seems to remain stationary, hence the long life of the cretins. In congenital athyroidism the disease is progressive and death takes place at a much earlier period than in endemic cretinism. As said before, no cases of congenital athyroidism have been known to live longer than thirty years. The results of opotherapy show that there are differences between congenital athyroidism, infantile hypothyroidism, and endemic cretinism. In the first two conditions the results of opotherapy are brilliant, whereas in endemic cretinism they are doubtful. Von Wagner claims that in endemic cretinism he has obtained brilliant results with thyroid opotherapy. On the other hand, Scholz, Kutschera, Bircher, and others claim that their results have been more or less negative.

As to the etiology of cretinism, we shall see in studying the causes of endemic cretinism and goiter that there is a marked divergence of opinion among writers. Some, as Kocher, von Wagner, von Eiselsberg, Langhans, and Seigirt, believe that this endemic cretinism is solely due to thyroid disturbances. "Without disturbed function of the thyroid, no cretinism," says Kocher. He believes that the same noxious causes producing other forms of hypothyroidism intervene during fetal life and cause cretinoid degeneration. This noxious agent primarily injures the thyroid, and secondarily all the organs. On the other hand, Bircher, Kaufmann, Scholz, Kutschera, and Dieterle believe that the thyroid disturbances are not solely the cause of the disease, but that there are other determining causes of cretinic degeneration.

One thing is certain: in every cretin the thyroid gland is not always atrophied, but is, on the contrary, in some instances, hypertrophied. Besides degenerated portions, such enlarged glands often possess others which seem to be normal, and which, so far as we can judge by their histological appearance, are undoubtedly capable of function. After going over cases of cretinism in which microscopic examination of the thyroid has been performed, we must conclude that there is not always a striking parallelism between the intensity of cretinism and the histological disturbances. As cretinism does not respond to thyroid opotherapy as readily as other forms of thyroid insufficiency, and on account of the above-mentioned reasons we can conclude with Ewald, Kutschera, Bircher, etc., that endemic cretinism is a physical as well as an intellectual degeneration not solely due to thyroid insufficiency, but to some additional damaging influences on the other organs of the body as a consequence of the endemism; in other words, the pathological agent of endemic cretinism is *polytrope* and not *monotrope*. This means that in order to have a true cretinism we must add to the disturbed thyroid function other causes. One of the most important of these causes is

the fact that "the goitrous endemism" has been exerting its nocive influence upon the organisms of these individuals throughout successive generations. The union of all of these conditions gives, then, rise to the true or endemic cretinism, whereas surgical and congenital athyroidism, spontaneous infantile, and adult hypothyroidism are caused only by a thyroid insufficiency and by no other cause.

In cretinism, as in the other forms of hypothyroidism, all degrees of development can be met with. If the noxious agent is of benign type the thyroid insufficiency will be a moderate one, and that condition may remain stationary throughout life. But if the damaging agent is more virulent and affects individuals already in unstable thyroid equilibrium, cretinism will be more severe. All the various stages found between the mild and the most severe forms of cretinism are only links of the same chain, and Fodéré was indeed correct when he said, "Goiter is only the first degree of a degeneration whose last manifestation is cretinism."

The goitrous endemism includes the *true endemic cretinism*, *endemic goiter*, *endemic deaf and dumbness*, and *endemic feeble-mindedness*. In opposition to what is seen in other forms of hypothyroidism, *males* are more often affected with cretinism than females.

**Symptoms of Congenital Athyroidism, Spontaneous Infantile Hypothyroidism, and Cretinism.**—As the symptomatology of congenital athyroidism, spontaneous infantile hypothyroidism, and cretinism, endemic and sporadic, on the whole resemble each other very much, I shall give the clinical description of these conditions in the same chapter in order to avoid unnecessary repetitions. I shall dwell on their respective characteristics in the chapter on Differential Diagnosis.

When any of the above-mentioned types of thyroid insufficiency has reached its full development the clinical picture is so striking, so characteristic that a glance is sufficient to make the correct diagnosis. When one has seen one case he has seen what is peculiar to all cases, no matter what the particular type may be. In the first place, there is on the small body of the dwarf, for such the patient will be, an enormous head entirely out of proportion to the rest of the body. If we add to this a vague, lifeless, stupid look with a cretinoid physiognomy the first impression is complete. As for details we may note that the skull is deformed, voluminous in the occipital, and narrow in the frontal regions, and that the anterior fontanelle is still persistent even in individuals fifteen to twenty years old. The face is round, in "full-moon," and without expression, the forehead low, receding, and furrowed with numerous wrinkles. The nose is wide at the base, but short and retroussé; in a word it is what we call expressively the "saddle-nose." The ears are thick and everted. Both malar regions are prominent; the cheeks, flabby

and hanging, while the lips are thick, cyanotic, and everted. The mouth is wide and open. The tongue, so thick that it is too large for the oral cavity, protrudes for much of the time from the mouth. Sometimes it hangs out constantly and a continuous flow of saliva may be seen running out at the corners of the mouth. This macroglossia is not due to muscular hypertrophy but is caused by an abundant deposit of fat and mucine between the muscular fibers; it is a sort of lipomatous macroglossia. In regions where goiter and cretinism are endemic the teeth are decayed, but in countries where goiter and cretinism are only spo-



FIG. 58.—A group of cretins. (Bainbridge.)

radic the quality of the teeth of these cretins, according to Bayon, does not differ very much from that of the teeth of normal children. Of course in congenital hypothyroidism teeth are absent, second dentition does not take place in most cases, and if it does, it occurs only very late, say at the ages of twenty-five to thirty years. The neck is short, and lipomatous masses are found in the supraclavicular spaces. The thorax is flat; the abdomen large and hanging, and has the shape of a "frog-belly." Umbilical hernias are very often present. The arms, legs, hands, and feet are very stocky, and the swollen fingers can be moved only with difficulty. The feet are short and deformed and too

broad for their length; the toes are swollen, and hence produce a peculiar, unsteady and obviously difficult gait. The skin is pale and sallow, semitranslucid, recalling a little the clinical picture of *phlegmasia alba dolens*. Even in a very advanced period of life the skin remains unbearded; the hair of the pubis and axillary regions does not grow, while the eyebrows and lashes are always spare and thin. The mucous membranes of the larynx, esophagus, and intestinal tract are edematous. The genital organs, atrophied and arrested in their development, retain the infantile type. If the male cretin reaches the adult age, his testicles and penis are considerably smaller than normally. The same is true for the uterus and its appendages in the female cretin. With such hypoplasia of the genital apparatus, sexual appetite is not present. The genital functions are more or less suppressed, and only after the thirtieth year do the genital organs seem to develop sufficiently to functionate; but fortunately these cretins are usually sterile.

*Nanism* is one of the earliest and most striking symptoms in athyroidism and spontaneous infantile hypothyroidism. The expected growth of the skeleton does not take place, or if it does it occurs very slowly. Normally the length of the skeleton is 172 cms. for man and 160 cms. for woman. In cretins the skeleton varies from 60 to 120 cms. in length. For example, the Pacha de Bicetre, nineteen years old, was only 90 cms.; the cretin of Batignolles, thirty-one years old, was 1 meter and 10 cms. long; the cretin of Francotte was 84 cms. long when twenty-one years old; and the one of Combe, 80 cms. when fifteen years old. The bones are thick and deformed, as in rickets, and deformities of the ribs and pelvis are frequently found. Kyphotic and scoliotic anomalies of the spine are quite common. The skull of the cretin is flat and low, and wider than it is high. The bones of the skull are thick, and prognathism is a characteristic feature.

All cases of congenital athyroidism are idiots. If athyroidism or hypothyroidism occurs at a later period of bodily development, then the degree of idiocy is in direct proportion to the period of development at which the thyroid function has become totally insufficient.

In congenital athyroidism and in the most advanced forms of cretinism the little patients live a purely vegetative life; they eat, breathe, and sleep, and that is all. They do not even have the instinct of conservation, for although suffering from hunger and thirst they do not have the intelligence to take the food that is placed near them, and if they should not be actually fed, they would starve to death. They sit for hours, motionless, inert, and entirely unconscious of the surrounding world, insensible to good or bad treatment, and incapable of recognizing even their parents. They are indeed what Roesch calls the "manplant."



If hypothyroidism manifests itself some time after birth, namely, after the child has undergone a certain degree of physical and mental development, the symptoms will be less accentuated. Such little patients do recognize their surroundings, and may even smile when they see their parents, thus showing that their cerebral system is able to register impressions, although in a very rudimentary degree. It is the vestiges of their early, but too soon interrupted cerebral education, that they show when they manifest signs of pleasure or discontentment, or when, for example, they make efforts to grasp toys lying nearby. Certainly they have sensations. Their psychic vacuum is not absolutely complete and they may even have perceptions. They have the instinct of conservation, since if food is placed near them they will take it. They manifest their emotions, and possibly their perceptions, too, by grunts and growls. As a domestic animal may be taught, so may they be taught to be clean, and they may even be trained to do things which require only a rudimentary intelligence, such as to carry wood or water. They correspond to what Roesch calls the "man-animal."

Of course between these extreme forms of hypothyroidism and cretinism all degrees are found. But, to continue, the organs of sense show a greatly diminished function; the senses of smell, taste, and touch are not acute; sensibility is considerably reduced. The cretin will stand for hours in the full glare of the sun and show no signs of being discomforted by it. Indeed, their eyes do not seem to be at all affected by the intense light. They hear and speak with difficulty, and quite often are deaf and dumb. Sometimes the speech consists only in a few inarticulate sounds which are understood only by members of the family; when more highly developed many seem to have an especially great difficulty in pronouncing the consonants. Their memory is weak. They are unemotional, and in their affections resemble animals. If anyone has been unkind to them they do not forget it. On the other hand, they rejoice very much when, as Kocher says, "They see a friend of their stomach." They are very sensitive to cold, for not only is the central temperature reduced, but the peripheric circulation is also diminished. The blood-pressure is low; pulse small and easily depressible. Their muscular system is always poorly developed; their strength is in proportion to their stature and their movements are slow and awkward. The "frog-shaped" belly which is often found in cretins is no doubt caused by this general relaxation of the musculature, and this relaxed condition plays an important part, no doubt, in the etiology of hernias which are so frequent in cretinism. Since they show a profound dislike for any physical effort, they sleep most of the time, and for hours will sit motionless in the same place. More than once in the hospital ward I have found them sitting at the same place where I had left them hours before,

in exactly the same posture, and totally indifferent to the external world. Their appetite is moderate, and they have a natural aversion to meat. Their digestion is bad, and, as a rule, they suffer from constipation. Cretins show great sensitiveness to the effect of alcoholic drinks. In regions where cretinism is endemic, every little town, so to speak, has its "cretin" and one of the greatest amusements of the unmerciful and heartless youth is to give a glass or two of wine to these poor creatures in order to intoxicate them and then to enjoy their contortions and queer faces.

**Differential Diagnosis.**—Since the symptoms of endemic and sporadic cretinism, congenital athyroidism, and spontaneous infantile hypothyroidism are so much alike, differential diagnosis is sometimes very difficult. In the majority of cases, however, it can be made.



FIG. 59.—A group of cretins.

Life in congenital athyroidism is ordinarily short. Death occurs most usually during the first two or three years. According to Ewald no case of congenital athyroidism is known to have lived longer than thirty years, whereas some endemic cretins have acquired notoriety by reaching the ages of fifty to sixty years, and even eighty-six years. In congenital athyroidism and spontaneous infantile hypothyroidism the myxedematous infiltration of the skin is very much more marked than in endemic cretinism. On the other hand, in the latter condition the retarded growth and deformations of the osseous system are less marked than in the former. A consideration of value in differentiating congenital athyroidism from cretinism is the fact that the latter condition occurs when goiter is endemic. To be sure, there are sporadic forms of cretinism seemingly occurring in regions where no endemism is present. As a

rule, however, we nearly always find in the ancestors of endemic and sporadic cretins, endemic goiters or other cretinoid conditions, serving as telltales.

In countries where cretinism is endemic, individuals who have goiter, who are of small stature, and at the same time have a certain mental deficiency, are called "cretins." This appellation is not exact, as such individuals are not actually "cretins" but *cretinoids*. They represent a higher step in the scale of cretinism where, in fact, all degrees of cretinic degeneration may be found. Certain individuals may, at the first glance, appear to be normal physically and mentally, yet their stature, which is slightly under normal, their wide face, with low forehead, and the prominence of the malar bones, the slight touch of "saddle-nose" and their limited intellectual power show that these individuals have been stamped, although lightly, with the goitrous endemism. One need only to walk through certain Swiss valleys to become convinced of the fact that there are many thus afflicted. Indeed, we may go so far as to say that in certain districts the entire population is marked with the endemism.

In the first year of life it is extremely difficult to diagnose cretinism or any other form of hypothyroidism. At that age the child lives a purely vegetative life; it is even difficult to decide whether the child is normal or not. In fact the only symptom which might point toward thyroid insufficiency is a thick tongue, protruding from the mouth, or unusually thickened integuments. Sometimes the disease takes such a slow course that the child reaches the second or third year before anybody realizes that something is wrong with it.

When studying the embryological development of the thyroid we saw that the thyroid gland at birth is formed by a mass of non-differentiated cells. No colloid is present, and only in a later period do these cells shape themselves into normal alveoli. During this cellular anarchy it is permissible to assume that the function of the thyroid is greatly disturbed, and that it is in a state of hypofunction. Some authors, as Langhans, Kaufmann, and Bircher, go so far as to claim that the fetal thyroid is normally physiologically inactive. They regard the maternal hypertrophy of that gland as a compensatory process caused by the lack of thyroid function in the fetus. Although it is highly probable that the function of the thyroid during fetal life is diminished, it is, nevertheless, difficult to admit that the gland is in a state of complete physiological negativism. Let us not forget that there is a period, the vesicular stage, during fetal life when well-formed alveoli containing colloid are present. Nothing proves that the thyroid at that time does not functionate. Furthermore, it is a well-known fact that pregnant women afflicted with hypothyroidism see their symptoms of thyroid insuffi-



ciency improve greatly during pregnancy. This is most likely due not only to the hyperplasia of their own thyroid but also to a compensatory function of the thyroid of the fetus.

The reason why symptoms of hypothyroidism become noticeable only after a certain period of time after birth and not at once, is still a debated one. Some think it possible that during nursing the milk of the mother contains thyroid products in insufficient quantity to supply the ones lacking in the newborn. What seems to corroborate this view is that the symptoms of hypothyroidism become noticeable at the weaning time. Cows' milk seems to have, although in a lesser degree, the same protective influence. On the other hand, when meat diet takes the place of milk alimentation, hypothyroidism symptoms progress very rapidly. It has been said that the thymus offsets the thyroid function during the first few months of the child's life, and then also becomes functionally insufficient. Possibly, too, the hyperplastic thyroid of the mother has left in the body of the newborn enough active principles of the thyroid to be sufficient for a certain period of time. Most likely, however, the best reason is that the symptoms of thyroid insufficiency are not, and cannot be recognized in their early development. Diagnosis is made only when they have acquired a certain intensity. Who can indeed say with a certainty that in a few months old child some of the manifestations of hypothyroidism, as for example myxedema and stupidity, are or are not present?

As a rule typical hypothyroidism is easily diagnosed. Some difficulty may be encountered in differentiating conditions which at first resemble those seen in thyroid insufficiency. For example, in certain forms of extreme chronic nephritis, of erysipelas of the face, when edema develops slowly and may cover large areas of the body, a doubt might rise in one's mind as to their true nature, but a closer examination will solve the problem. At the time of menopause a transient edema may be seen, especially in the face. It was considered by Dalché as of ovarian origin and was called by him *ovarian pseudomyxedema*. The same author has described a form of cutaneous infiltration of syphilitic origin and called by him *syphilitic pseudomyxedema*. In the *familial trophedema* Meige described a form of cutaneous infiltration which must be regarded as of trophic origin. Certain forms of scleroderma might, at a superficial glance, be mistaken for myxedema, but a more accurate examination and palpation of the neck will dissipate all doubts. *Adipose degeneration of genital origin* and the one seen in tumors of the hypophysis may sometimes be confused at first with myxedema, yet a careful examination of the genital apparatus and the feminine aspect of the individual will direct the attention toward genital hypoplasia. In tumors of the hypophysis the presence of headache, symptoms of



compression on the brain, aided by an x-ray of the skull will clear up the diagnosis.

Dercum and Henry have described areas of a diffuse general lipomatosis more marked in certain regions of the body, as in the arms or back. This condition is accompanied by symptoms of neuritis and is very painful to pressure. It is called *adipositas dolorosa*. Perspiration may be diminished or absent. Such cases may be very difficult to differentiate from myxedematous conditions, but the normal psyche, the absence of edema in the hands and feet, in short, the general aspect of the patient will prevent the mistaking these conditions for such as are due to thyroid insufficiency. When doubt still exists, the thyroid treatment will throw some light upon the subject; *adipositas dolorosa* does not respond to thyroid ootherapy.

All forms of dwarfism are not by any means symptomatic of hypothyroidism. *Microsomia*, for instance, a condition in which individuals, although of very small stature, are perfectly proportioned, has nothing to do with thyroid insufficiency. As Bayon says, "It is a *lusus naturæ*, a stunt of nature." Bayon divides microsomia into *congenital* and *infantile*. In the congenital form the child is born extremely small, whereas in infantile microsomia the child is normal at birth, but for some unknown reason remains of extremely small stature. In both forms the different portions of the body, although remaining very small, are still proportionate one to another. Daniels and Philipp compare one in these states to "a little man seen through the wrong end of an opera glass."

The great majority of dwarfs seen in vaudeville theaters belong to the infantile microsomia. Such dwarfs continue to grow gradually for thirty-five to forty years, and often so much so that after a certain period of usefulness on the stage they are discarded because they have grown "too tall."

Cases of *chondrodystrophia fetalis*, *microsomia*, or *achondroplasia* have been regarded in some instances as cases of cretinism. But if *chondrodystrophia fetalis* were in relation to thyroid insufficiency, it certainly should be found much oftener in regions where goiter and cretinism are endemic. This is not the case. In fetal chondrodystrophia, if the children are not born dead, a careful examination shows that in such conditions symptoms of hypothyroidism are wanting. The skin is not infiltrated; constipation is not present; temperature is normal; the thyroid gland can be easily palpated, and the only deformity found is that the long bones are too short in proportion to the skeleton. In further development, the intelligence and genital apparatus of such patients prove to be normal. The whole clinical picture is due to a malformation of the cartilages and not to the thyroid insufficiency. The bones grow normally in thickness but not in length.

In *infantilism* the osseous system and the soft parts of the body undergo their normal development; puberty only does not appear and the young individual retains an infantile appearance. In recent years Brissaud, of Paris, and his pupils have described a form of *infantilism* characterized by a persistence of the juvenile state as to body, intellect, and sexuality. The face is round, the body plump, and the extremities small: that is the Brissaud type. In other cases the body has a slender shape, the extremities are thin, the face delicate; that is the Lorain type. These conditions have nothing to do with thyroid insufficiency.

There are some idiots who present a certain likeness to the Mongolian race. This pathological class has been called *Mongolism*. The mongoloid has an inward and downward slanting of the converging palpebral fissures. He has some intelligence and is able to utter more or less distinctly a few words. The tongue is not thickened. In opposition to the real cretin, who remains sometimes for hours motionless. Mongoloids always show a certain restlessness in their manner. The abdomen is distended on account of obstinate constipation. The large fontanelle closes between the first and fifth years of life. Very often they have the saddle-nose as found in cretins. They are chicken-breasted. There is a great difference between the skeleton of the mongoloid idiot and the genuine cretin. In the first case the development of the bones is complete, while in the second they are considerably retarded. This can be easily demonstrated by an x-ray picture.

The skin of the mongoloid has no myxedematous appearance. The hair and nails are normal. Pfaundler and Schlossmann say: "The intelligence, which is from the beginning only slightly developed, has a tendency to continue on a low level, but still a distinct development is present. The speech is deficient, notwithstanding that the mongoloids understand their surroundings very well. They are unclean for many years and never reach the degree of intelligence that appears in the majority of cases of myxidiocy under thyroid gland therapy. A short comparison best shows the great difference between mongoloids and myxidiots. The mongoloid has no symptoms of myxedema in later years, no dwarfish growth, no apathetic, motionless manner, and none of the cessation of bodily and mental development peculiar in the myxidiot. He is uncommonly lively, dentition is normal, and he never shows the frightful, repulsive appearance of the myxocretin. Thyroid therapy affects them absolutely differently. The mongoloid reacts only in the beginning stage, not in psychic behavior. Teething, fontanelle closing, obesity, protrusion of the tongue are immediately and strikingly improved in the myxidiot, only partly, often not at all, in the mongoloid."

According to Bayon, in *microcephalia* the patients have a normal stature, but the cranial circumference is below 52 cms., and they pos-

sess a brain whose weight is less than 1100 gms. These measurements, however, have really no great importance. More than once the brains of the most hopeless cretins have been found to have the same weight as a normal brain, whereas people with normal or even superior intelligence have been known to have brains quite below the normal weight.

*Microcephalia* should not be confused with hypothyroidism, as in the first instance the cranium is small, whereas in athyroidism and cretinism the skull is abnormally large for the small stature. As a rule the microcephalic patients are alert and vivacious, which is just the opposite to what is found in cretinism. Furthermore, no myxedema is found in microcephalia.

*Hydrocephalia* has been confused sometimes with hypothyroidism and cretinism, yet this condition has no etiological relation whatever to thyroid insufficiency.

*Rickets* has been mistaken, too, for cretinism, and Hertoghe declares infantile hypothyroidism and rickets to be identical pathological processes. A closer examination of these two conditions soon convinces one that such a statement is not true. In rickets the cartilage between the shaft and the epiphysis of the long bones is greatly thickened, the line of ossification very irregular, more spongy and more vascular than normal. Beneath the periosteum, which strips off easily, there is an osteoid tissue resembling decalcified bone. In cretinism the cartilages are thin, and poorly supplied with bloodvessels; the line of ossification is very regular and linear. In rickets the intelligence of the patient is intact and the thyroid is normal. As Bayon says, "Rachitism is a disease of civilized centers, while cretinism is a disease of the poor, ignorant villages scattered in the mountains and valleys." Of course both conditions might be encountered in the same individual.

## CHAPTER XVI.

### SMALL THYROID INSUFFICIENCY.

BESIDES the glaring symptomatology due to absence or diminution of thyroid function which, as we have just seen, produces all forms of hypothyroidism and cretinism, there is a train of symptoms, more mild and less conspicuous, caused by a mild degree of thyroid insufficiency. Just as, for example, in renal disturbances, besides the big, more obvious symptoms of renal insufficiency, there are small, less apparent ones, so the same is true in hypothyroidism. Besides the big class of symptoms of thyroid insufficiency we find another class scarcely sketched, or very atypical. To the first class belong athyroidism, hypothyroidism and cretinism; to the second class belongs the *small thyroid insufficiency*.

What is true for all the glands of the body as the ovary, liver, etc., is true, too, for the thyroid; it may be congenitally weak. Although sufficient to meet the ordinary physiological exigencies, the thyroid soon becomes insufficient when confronted with increased physiological demands such as in menstruation, pregnancy, infections, etc.; hence symptoms of hypothyroidism.

In small thyroid insufficiency, the symptoms are various and multiple. They are never all present at the same time. Some may be found in earliest infancy, such as constipation, flatulence and somnolence, as well as others in a later period of life, as baldness, somnolence, and constipation. These symptoms are *sometimes, not always* due to thyroid insufficiency. Women are more predisposed to them than men. Heredity is also of importance, as it is not infrequent to find symptoms only mildly sketched in the mother, while they are more intensified in the children; the reverse may be true, too. I have seen a family in which all degrees of thyroid insufficiency could be found, from the mildest degree to a well-developed infantile hypothyroidism. The symptoms of thyroid insufficiency were so mild in one member of the family that almost everyone would consider it as a joke of very bad taste to call that patient thyroidly insufficient. Yet the small symptoms of thyroid insufficiency which she complained of were very suggestive, and were relieved by thyroid opotherapy.

The part played by consanguinity in the development of hypothyroidism has been well demonstrated by Hertoghe.

Caloric disturbances such as cold extremities, sensation of chilli-



ness, etc., are regarded by Hertoghe, Gauthier, Levi and Rothschild as of thyroid origin. Such patients are very sensitive to cold seasons, are never warm enough in summer, do not like drafts and complain of rheumatic pains and neuralgia.

Certain *gastro-intestinal disturbances* must be referred to insufficient thyroid function as, for instance, lack of appetite in certain children. Such young patients do not enjoy their meals, they care much more for sweets and, as a rule, do not like bread. Constipation is one of their chief complaints. Constipation due to thyroid insufficiency does not differ materially from constipation due to other causes. Its supreme test is thyroid treatment. It is found in every stage of life and in both sexes, and is characterized by a small stool, composed of hard, dry fecal matter. It would be an error to claim that every constipation is due to thyroid insufficiency. When, however, every other therapeutic measure has failed, and especially if at the same time some other small symptoms of thyroid insufficiency are present, the thyroid treatment must be given a trial. As was demonstrated by Marbe in dogs with intestinal fistula, thyroid opotherapy increases the secretions of the intestinal canal, and hence its evidently good influence on constipation. Possibly, too, the thyroid has an elective influence on the neuromuscular centers of the intestinal tract.

As seen in the chapter on Physiology, the relations between the thyroid and the *sexual apparatus* cannot be denied. We know that normal development of the genital organs goes more or less hand in hand with a normal condition of the thyroid. This has been abundantly demonstrated clinically and experimentally as in athyroidism and cretinism where menstruation remains absent and puberty is considerably retarded.

On the other hand, during menstruation the thyroid becomes congested and enlarged. This explains why during menstruation some women complain of a choking sensation and show Basedow symptoms.

On the other hand the relations between the thyroid and pregnancy are well known and the hypertrophy of the thyroid seen in pregnant women is not only due to hyperemia, but is also caused by a true hyperplasia. Gauthier, Parhon and Goldstein have shown that the thyroid and ovaries seem to be antagonistic—the more active the thyroid the less active is the ovarian function. Inasmuch as during pregnancy the ovarian function is suspended, the thyroid function is increased. This would explain why hypothyroidism is considerably ameliorated during pregnancy. Of course, the thyroid of the fetus may account, too, for this amelioration.

At the time of menopause when the ovarian function ceases, the thyroid flares up and becomes hypertrophied, causing nervous and psychic

disturbances to appear. However, after menopause has become a well-established fact, the thyroid gland may undergo atrophy; hence symptoms of hypothyroidism.

In conclusion we can say that the relations between the thyroid and the sexual apparatus are very intimate. We must, consequently, expect to find conditions in the genital apparatus of women, which, although at first seemingly atypical for hypothyroidism, are nevertheless etiologically related to it. Let us see if this is true.

It is common to see young girls apparently normal in whom puberty is retarded. In some of these cases of retarded, momentarily suspended or even totally suppressed menstruation, this hypo-ovarism is due to hypothyroidism. Infantile uterus accompanied by hypoplasia of the ovaries and of the entire genital apparatus might be regarded, too, as a consequence of hypothyroidism. Premature menopause followed by subinvolution of the genital apparatus, in other words, premature senility of that system, may also be regarded as a consequence of hypothyroidism. In some cases the disturbances are not objective, but only functional. Typical, for instance, is the case reported by Levi: A lady, aged thirty years, who since her puberty had menstruated but four or five times a year, and who complained of baldness of the masculine type. She was regarded by this author as a case of hypothyroidism and treated accordingly. Soon after treatment menstruation became regular, and remained so. In the same class is the case reported by the same author of a young girl, nineteen years old, whose menstruation was constantly retarded or absent, but which became regular after thyroid opotherapy.

Menstruation, instead of being retarded or absent, may be advanced, very abundant, and may last too long a time. In such cases menstruation is transformed into menorrhagia. In other cases menstruation is advanced and abundant, but its duration is not increased. At other times there is, as in one of my cases, a constant sero-bloody discharge lasting for years. Dysmenorrhea, when no other cause can be found, may be regarded as a form of thyroid insufficiency. Sterility, too, may be in certain cases benefited by thyroid opotherapy. Hertoghe believes that sometimes abortions, when not due to syphilis, tuberculosis, or some other cause, may be regarded as some manifestation of hypothyroidism. These views are corroborated by the fact that in endemic goiter and cretinism, abortions are extremely frequent.

Hertoghe also believes that retarded growth of the *osseous system* in rickets, heredosyphilis, etc., is directly or indirectly due to thyroid insufficiency. Infections and intoxications affect primarily the thyroid, hence their influence on the growth of the skeleton. Gauthier was the first to call attention to the fact that *retarded consolidation in fractures* might, in certain instances, depend upon thyroid insufficiency. Here,

again, before using the medication, every other possibility, such as interposition of muscular fibers between the fragments, syphilis, etc., which might interfere with consolidation, should be carefully investigated, and only when everything has failed should thyroid medication be resorted to.

Certain forms of *dermatosis* such as acne, herpes, eczema, psoriasis, scleroderma, etc., may in certain instances depend upon thyroid insufficiency. This to a certain extent seems plausible, as we know that the thyroid has an undeniable influence over the nervous system and the metabolism in general.

A number of other conditions might be regarded as the consequence of thyroid insufficiency. It would take me too far to go into more details. Those who might be interested in these questions may look them up with great benefit in Hertoghe, G. Gauthier, Levi and Rothschild.

I should not like to be understood as saying that every case of retarded consolidation, every trouble of the genital apparatus, every disturbance of the gastro-intestinal tract, or every skin disease is the consequence of thyroid insufficiency, and that thyroid treatment is the only one indicated in such conditions. I say only that, according to my knowledge along that line, and according to the wide experience of such other authors as Hertoghe, Gauthier, Levi and Rothschild, there are certain conditions which may be greatly benefited by thyroid treatment; this treatment, however, should be resorted to only when a careful differential diagnosis with other possibilities has been made, and only when other therapeutic measures have failed. In certain instances the facies of the patient, his mental development, an exaggerated adiposity, or some other symptoms of thyroid insufficiency may point out the real cause for the pathological conditions with which one is confronted. But many other times no sign of hypothyroidism whatsoever is found which might put the physician on the right track. In such cases, if every other therapeutic measure has been tested, it will do no harm, and may do a great deal of good, to try thyroid treatment.

## CHAPTER XVII.

### ETIOLOGY OF ENDEMIC GOITER AND CRETINISM.

**Historical.**—Despite all modern investigations and researches the etiology of *endemic* goiter still remains one of the most obscure of medical problems. The disease is probably as old as the human race and is mentioned in the literature of the earliest people. The Atharva Veda, an ancient Hindu collection of incantations dating 2000 years before Christ, contains extensive forms of exorcism for goiter.

It is evident from the writings of Vitruvius and Juvenal that goiter was known to them. Vitruvius says, “Guttur homini intumescit praesertim apud agricolas Italiae et medullos Alpinos.” (Maurienne et Tarentaise). Juvenal writes in a passage of his Satires, “Quis tumidum guttur miratur in Alpibus.” Marco Polo relates in his travels (13th century) that goiter is prevalent in the plateau of Central Asia. During the Renaissance the observations of the Swiss physician and alchemist Paracelsus (1493–1541) are especially noteworthy not only because of his excellent description of the malady in the region of Salzburg, an important focus to this day, but also because therein attention is first called to the existing relationship between goiter and cretinism, and the earliest positive information given concerning the latter disease. The literature of the 16th and 17th centuries offers little of interest on this subject. Hirsch gives a list of authors who report concerning the occurrence of goiter and endemic goiter centers in the Alps, in the Pyrenees, in Hungary, in the Atlas Mountains, in Peru, in Guatemala, in Sumatra, in the Harz, and Riesengebirge, etc. None of such writers, however, treated the subject from a more comprehensive point of view or studied the question scientifically. It is true that in 1779 Saussure furnished us with some interesting observations in his *Voyage dans les Alpes*, but we are indebted to Malacarne of Turin, for the first scientific treatment of the subject in the report of his observations in the Valley of Aosta, published in 1789 (Torino, 1789, *Sui Gozzi e Sulla Stupidita*). In 1793 appeared Fodéré's basic essay on *Goiter and Cretinism in the Maurienne and Aosta Valley*, and in 1800 his *Treatise on Goiter and Cretinism*. Following closely upon this we have the work of Coindet and Maunoir at Geneva (1815–1822); of Rambuteau, Imperial Prefect in the Valais, and of Iphofen in Saxony (1810–1818).

Toward the middle of the last century the importance of the ques-



tion from a sociological point of view was officially recognized, and in 1848 the Sardinian Government named a commission for the purpose of investigating the causes of endemic goiter and of finding a remedy for the disease. This example was followed in 1864 by the French Government. These commissions, after several years of research, produced elaborate reports which threw little new light upon the question but seemed to establish as a scientific fact the popular belief in the hydric origin of goiter.

Since early in the 19th century there has accumulated such a wealth of goiter literature that it is impossible to enumerate all of these publications. In the Index Catalogue of the Surgeon-General's Office, U. S. Army, not less than 1857 publications are enumerated under Cretinism, Goiter and Thyroid Gland. Recently, M. Scholz mentions 2486 publications concerning cretinism alone. A. Hirsch, in his *Study of the Historical and Geographical Relations of Goiter*, has given an admirable and in many respects still unsurpassed recital of the historical development and various endemic and epidemic occurrences of the disease. In 1908 Switzerland created a goiter commission presided over by M. Schmidt, Director of the Federal Bureau of Hygiene, Berne. Italy has recently followed this example, and both commissions are supposed to work along experimental lines which cannot fail some day to throw light upon this still obscure question.

**Geographical Distribution of Endemic Goiter and Cretinism.**—Perhaps to no other disease can the term *endemic* be so appropriately applied as to goiter. Entire districts are so intensely affected that a large proportion of the inhabitants are goiter-bearers, the disease affecting animals as well as human beings. The limitations of the areas subjected to the endemism are so sharply defined that sometimes a hill, river or even a street may form the dividing line between the goitrous locality and immune territory.

Further demonstration of the localized character of the malady can be found in the numerous examples of individuals from goiter-free districts who rapidly acquire thyroid enlargements while living in regions of goiter endemicity, and who recover on removing to immune territory, or *vice versa*, in the numerous cases of goiter-bearers who remove from the endemic region sufficiently early in the development of the disease before colloid and cystic changes have ensued in the gland, when the possibility for the struma to disappear still exists. Thus, according to Guyon, emigrants from the Canton of Valais lost their goiters in Algiers; and Hubner reports that 16,000 emigrants from the district of Salzburg, in general goitrous, saw this infirmity disappear after settling in Prussia. Cardinal Billiet writes, "When an infected family moves to a parish not in endemic territory, such goiters as are not too severe, dis-

appear gradually, and in the second or third generation, this family will acquire normal thyroid glands."

Endemic foci are distributed over all the inhabited portion of the earth's surface. So closely associated with goiter is the distribution of cretinism that the geographical occurrences of both forms of disease cannot be easily separated, and are most comprehensively and adequately treated together. In Europe the center of highest endemicity for goiter and cretinism is to be found in the Middle Alps, whence it radiates in diverse directions. There are numerous other foci in connection with different ranges or deep-lying river valleys as the Carpathian, Pyrenees, etc. But even within these areas the endemism is not uniformly distributed.

In Switzerland, the Canton of Valais, the valleys of the Rhone and its tributaries are centers of high endemicity. The Valley of the Reuss in the Canton of Uri and the Valley of the Aare in the Canton of Aarau are severely affected. The endemism is most intense in the Cantons of Berne, Argovy and Fribourg; no canton, however, is completely immune. According to Bircher, from 22 to 50 per cent of the school children and from 15 to 30 per cent of the recruits are goitrous in the districts on the right bank of the river Aare. The statistics furnished by Kocher show from 80 to 90 per cent of the school children of Berne to be goitrous.

The endemism is intense in the valleys radiating from Mont Blanc into Lombardy, and from the Alps of Savoy into the neighboring departments of the Basses-Alps, the Maritime Alpes, the Haute-Garonne, etc., where both goiter and cretinism are prevalent.

The extent of the social and economic loss due to the goiter endemic in European countries is scarcely appreciated. As we know, goiter and cretinism go hand in hand. As early an observer as Fodéré remarked that "Goiter is the first degree in a degenerative process of which cretinism is the last step," and since then the majority of scientific investigators have adopted the same conclusions.

Fodéré, Maffei, Roesch, Traxler, Morel, Lombroso, Milani, Marchant, Lourdes, Koestl and Chabrand consider the causal factors of both diseases identical. Maffei calls goiter the "precursor of cretinism," Roesch considers it the "first link in the chain of degrees and forms of cretinism," Morel says that "goiter is the first stage on the road that leads to cretinism," and Niepce refers to goiter as the "first degree in the degenerative process of which cretinism is the final term." Other investigators lay more stress upon the etiological relationship, believing that where the endemism is light, goiter alone is to be found, and that where it is severe, cretinism appears. Rambuteau says, "The causes of goiter and cretinism are the same, and only differ in the degree of activity," and Milani affirms that "where only goiter is to be found, we can be

certain that the endemism is mild." We may therefore conclude that where goiter is at home, cretinism is rarely missing, and in regions of high endemicity it is frequent. This is true not only of the Central European Alpine region, but also of the high plateau of Middle Asia and all other goiter regions of the earth. This local and geographical joint occurrence indicates, of course, an intimate connection between the conditions of both maladies. Griesinger writes: "Where the endemic is very severe, the entire population is affected. Besides the true cretins, the half-cretins and goiter-bearers, there are innumerable weak-minded, miserable and badly proportioned individuals; there are many deaf-mutes, stutterers and stammerers, and strabismus and deafness are frequent. Through the entire native-born population runs a streak of physical degeneration and mental dulness; even those individuals who pass for healthy and intelligent, are, on the whole, unlovely, narrow-minded and sluggish, and the country teems with mean-spirited philistines in whom the qualities of heart are insufficient to compensate for the lack of intellect."

Often the influence of the cretinoid degeneration is to be observed only in symptoms to which ordinarily no significance is attached; they are considered as racial peculiarities or family characteristics, etc., but not as the sign of a pathological process, which they really are. Among these symptoms must be classed, abnormally small stature with disproportionately long body and short legs, ugly repulsive features, mean-spiritedness, diminished mental faculties, retarded developments, etc.

Close observers have long ago noted that these peculiarities are not accidental, but stand in close relationship with the prevailing endemic goiter and cretinism.

That *deaf-mutism* must be included in the cretinoid degeneration has been scientifically established by the investigations of Bircher and others. Deaf-mutism is to be found elsewhere than on endemic territory, but is of rare occurrence and is not associated with idiocy. In countries exempt from goiter there occur 3 cases of deaf-mutism per 10,000 inhabitants, while in endemic centers it is far more frequent. Among civilized countries, Switzerland possesses the highest number of deaf-mutes. The statistics of 1871 show a general average for the whole country of 24 per 10,000 inhabitants. Were we, however, to separate the endemic territory from the rest of the country, the relative figures would be far higher, amounting in some regions to 250 and more per 10,000 inhabitants.

In Austria, the regions where severe goiter endemism prevails suffer proportionately from an endemic deaf-mutism; in Salzburg there are 27.8 deaf-mutes per 10,000; in Styria 20, and in Carinthia 44 per 10,000. The endemism is most intense in the Carinthian district of St. Veit and Wolfsberg and in the Salzburg district of Zell, where there are more than 50 deaf-mutes per 10,000 inhabitants. This coincident and parallel

movement points to a close inner relationship. These statistics as to endemic deaf-mutism have been drawn from H. Bircher's monograph on *Endemic Goiter and its Relationship to Deaf-mutism and Cretinism*. His conclusions are, "We must consider endemic deaf-mutism not only as an accompanying symptom of cretinism, but also as an intermediate form of the cretinoid degeneration between goiter and cretinism." He further says, "It is my belief that endemic goiter, deaf-mutism and idiocy are only different degrees and ultimate results of one and the same degenerative process." Moreover, the endemics of these diseases are invariably concurrent, that is, the severer forms of the degeneration such as deaf-mutism and idiocy do not occur without the milder form—goiter. But where the endemism is slight, goiter may occur without deaf-mutism and cretinism. In conclusions based upon investigations made in the deaf and dumb asylums of Switzerland, Bircher states that while two-thirds of the pupils in these asylums are cases of endemic deaf-mutism and one-third sporadic, it is safe to affirm that 80 per cent of all deaf-mutism in Switzerland must be attributed to the prevailing goiter endemism. Of the pupils in Swiss asylums for the deaf and dumb 72 per cent are goitrous.

In the Provinces of Piedmont, Lombardy and Venice, in 1883, among a population of 9,565,038 there were 128,730 goiter-bearers and 12,882 cretins. That is, about 1 in every 67 of the inhabitants was either goitrous or cretinous.

In the Tyrol the statistics made by the Austrian Government in 1883 show 930 cretins in a population of 797,040; the number of goiters is not given. In Cisleithania, Austria, with a total population of 21,840,112, there were in 1883, 12,815 cretins, or 58.6 per 100,000. In the District of Murau in Styria, where the endemism is most intense, the proportion of cretins is 1045 to every 100,000 inhabitants. In France, Baillarger estimated in 1873 that the total number of adult goitrous individuals over twenty years of age reached 370,043, and that of cretins about 120,000; that is, in a total population of 36,000,000 the proportion of goiter subjects was 1.04 per cent and that of the cretins, 0.33 per cent. These figures, however, change most significantly if we consider the regions where the endemism prevails with the greatest intensity separately; we then find in the department of Savoy, for instance, 133.7 goiterous individuals per 1000, and in the valleys of the Maurienne and Tarantaise respectively, 22.7 and 14.5 cretins per 1000.

According to the statements of Mayet in 1900 these conditions as given by Baillarger have not altered appreciably. McCarrison reports that in the part of the Himalayas where his researches were carried out, goiter is so common that in some of the villages it is difficult to find man, woman or child not suffering from the deformity. He estimates



that not less than 20 per cent. of the population of Gilgit suffer from goiter, and he found in a population of 70,000 over 200 cretins. In Himalayan India and Europe alone McCarrison estimates the number of sufferers from goiter at about 5,000,000. In fact it cannot be sufficiently emphasized that goiter exercises an eminently destructive racial influence, and that where it is endemic the capacity for physical and intellectual work must be seriously undermined. Nor must it be forgotten that the mortality for endemic centers is considerably higher than elsewhere.

In Tyrol, Carinthia and Styria there are numerous goiter and cretin centers, the disease descending from the mountain slopes into the plains and appearing here and there along the river valleys such as the Danube, Enns, etc. Despite the very striking association of goiter with mountainous regions, it is not confined to them. St. Lager tells us that it is prevalent on the plains of Lombardy, of Piedmont, and of Alsace; that it occurs on the plains of the Danube in Upper and Lower Austria, and that it is met with on the plains of the Lena and Obi in Russia and along the St. Lawrence River in Canada; and that it is even to be found in some of the oases of the Sahara. Goiter is very rare in the North German Lowlands, in Denmark, the Netherlands and in the Scottish Highlands. In Sweden, according to Ewald, there existed in the whole country in 1867 only 628 goiter-bearers, of which 579 were to be found in the District of Falun. In France the Alpine Departments, the Vosges, Cevennes, the Pyrenees and the high central plateau are affected. In 1918, Kjolstadt relates that goiter was extremely prevalent in the Teemarken district in southern Norway, southwest of Christiana, and that in one school at Lunde 80 per cent of the children had goiter.

The disease is so common in certain parts of England that it has been known as the "Derbyshire neck." It is especially prevalent in Derbyshire, Hampshire and Sussex. In Spain endemic centers exist in the Pyrenees, Asturia and Galicia. The mountains of Asia, Japan and many of the Asiatic Islands have numerous foci. The Himalayas, the Cordilleras, Caucasus, Ural, Atlas and Altai Mountains all have goiter centers. Goiter occurs also upon islands like Ceylon, Madagascar, the Azores, Java and Sumatra.

In South America the first explorers of New Granada were astonished to find the banks of the Rio Magdalena inhabited by a race of heavy and stupid savages of sluggish habit who passed their days in sleep. Among the goitrous Indians of the Peruvian plateau, cretinism had reached such a degree that it required nothing less than a papal bull from Paul III to convince the missionaries that these were indeed men with souls to be evangelized.

In Brazil the river which divides the provinces of Corrientes and Entre-Rios is called the Guay-qui-raro or "thick-neck maker" by the

Indians, a convincing testimony as to the existence of the endemism in these regions.

In the Balkans the Struma River, along which heavy fighting took place during the great World War, is called "Struma" because of the prevalence of goiter along its banks and tributaries.

It has been asserted by Saussure and Demme that goiter was not to be found above an altitude of from 3000 to 3600 feet, and Demme and Maffei maintain that it does not occur under 900 feet. We know both of these theories to be untenable. McCarrison met with goiter at 10,000 feet in the Himalayas, and we have reliable information as to its existence up to an altitude of 15,000 feet (Nepal, Kemaon, Kashmir, etc.), and at 6000 feet in Savoy as well as on the high plateaus of Bolivia and Peru.

The mountainous regions of the Upper Tonking, Laos and Yunnan, as shown by Clavel, Simon, Billet and Jouveau-Dubreuil, may be considered as one of the great boulevards of goiter just as severely affected as the Alps and Himalayas. In 1896, Billet wrote of Kao-Bang, "This affection is extremely common among the native population inhabiting the rocky amphitheaters and deep gorges of Upper Kao-Bang."

**Geographical and Racial Distribution of Simple and Thyrotoxic Goiter in the United States.**—Goiter is to be found in North America, where Munson has observed closely circumscribed endemics among the Indians. Three hundred and ten Indian students representing forty-three tribes from six states of Alaska were observed by Kerr, in 1919, and it was found that 10.6 per cent showed a definite enlargement of the thyroid. This survey showed that in full-blooded Indians the existence of goiter is very uncommon as compared with its presence in those with part Indian blood or in the pure Caucasian race.

According to Bircher (who gives St. Lager as his authority), endemism and deaf-mutism prevail in the states of New York, Ohio, Virginia, Michigan, Kentucky, Tennessee, Maine, Vermont, Connecticut, Massachusetts and New Hampshire. There are 15,000 feeble-minded in Ohio. In Wisconsin endemic goiter is common. The region of the Great Lakes is reported by Dock, Osler and Adami to have numerous goiter centers. Ashmead tells of an endemic center in Pennsylvania, and Holder, of centers in Montana, Dakota, Mississippi, and also in the vicinity of the Rocky Mountains. Marine finds the disease widely disseminated along the Great Lakes, not only among human beings, but also among animals. He states that the endemism is especially severe among sheep. According to his investigations, 90 per cent of the street dogs of Cleveland are goitrous. In the United States and Canada, goiters though numerous, are as a rule, not large, and cretinism is rare. Along the shores of Lake Erie, Adami speaks of French-Canadian villages in which scarcely a family is to be found without one or more goitrous members.

It is, however, only since the Great War that we have been able to get a clearer insight into the goiter conditions prevailing in the United States. The following facts and conclusions have been taken from the statistical information given out by the War Department in 1920. For the sake of clearness, the information concerning both the simple and thyrotoxic goiters have been handled together in this chapter.

Out of 2,510,791 men examined for military service a surprisingly large amount of goiter, both simple and exophthalmic, was found. Of simple goiter, there were 11,971 cases recorded and of exophthalmic goiter 8647 cases, making altogether over 20,000 cases. This is a little less than 1 per cent of the population examined. Of cases of simple goiter over one-fourth (3100) were rejected for all military service primarily because the neck was so large as to interfere with the wearing of the military uniform. The remainder were mostly accepted for general military service. In the case of the more severe exophthalmic goiter of the 8647 cases found, 7985 were rejected for all military service, making 93 per cent. There were, however, 375 surgical defectives who were regarded as qualified for general military service.

GRAND TOTAL FOR GOITER, EXOPHTHALMIC, WITH RATIO PER 1000 MEN.

State.	Number of cases.	Ratio per 1000.	State.	Number of cases.	Ratio per 1000.
Washington . . . .	335	9.42	North Carolina . . .	106	1.91
Wisconsin . . . . .	502	7.94	California . . . . .	157	1.95
Alaska . . . . .	9	7.39	South Carolina . . .	68	1.73
Michigan . . . . .	682	6.89	Nebraska . . . . .	50	1.70
Oregon . . . . .	102	6.37	Georgia . . . . .	103	1.61
Illinois . . . . .	999	5.57	New Jersey . . . . .	117	1.54
Ohio . . . . .	726	5.08	Connecticut . . . . .	55	1.53
Pennsylvania . . . .	973	4.81	Nevada . . . . .	5	1.52
Missouri . . . . .	411	4.80	Kentucky . . . . .	88	1.38
West Virginia . . . .	176	4.52	Rhode Island . . . .	18	1.24
Vermont . . . . .	36	4.28	Arizona . . . . .	8	.96
Virginia . . . . .	222	3.99	New Hampshire . . .	8	.94
Utah . . . . .	45	3.82	New Mexico . . . . .	9	.88
Colorado . . . . .	81	3.60	Oklahoma . . . . .	53	.87
Maryland . . . . .	133	3.57	Maine . . . . .	17	.86
District of Columbia .	40	3.47	Mississippi . . . . .	30	.80
North Dakota . . . .	61	3.41	Alabama . . . . .	41	.79
Montana . . . . .	93	3.39	Delaware . . . . .	4	.79
Minnesota . . . . .	243	3.38	Louisiana . . . . .	39	.75
Idaho . . . . .	40	3.20	Florida . . . . .	16	.66
South Dakota . . . .	66	3.18	Massachusetts . . . .	58	.63
Indiana . . . . .	223	3.12	Arkansas . . . . .	16	.37
New York . . . . .	757	2.94	Texas . . . . .	42	.34
Iowa . . . . .	196	2.86	State not specified .	137	1.44
Kansas . . . . .	106	2.76			
Wyoming . . . . .	18	2.71	Total . . . . .	8647	3.14
Tennessee . . . . .	127	2.07			

## GRAND TOTAL FOR GOITER, SIMPLE, WITH RATIO PER 1000 MEN.

State.	Number of cases.	Ratio per 1000.	State.	Number of cases.	Ratio per 1000.
Idaho . . . . .	336	26.91	Kentucky . . . . .	90	1.41
Oregon . . . . .	421	26.31	District of Columbia	16	1.39
Washington . . . . .	832	23.40	Kansas . . . . .	48	1.25
Montana . . . . .	576	21.00	Arizona . . . . .	10	1.21
Utah . . . . .	185	15.72	New York . . . . .	308	1.19
Wyoming . . . . .	102	15.37	Maryland . . . . .	35	.94
Wisconsin . . . . .	886	14.02	South Carolina . . . . .	37	.94
Alaska . . . . .	16	13.14	Connecticut . . . . .	32	.89
Michigan . . . . .	1,131	11.43	New Mexico . . . . .	9	.88
North Dakota . . . . .	156	8.73	Oklahoma . . . . .	44	.72
Minnesota . . . . .	578	8.04	New Hampshire . . . . .	6	.70
West Virginia . . . . .	307	7.89	Maine . . . . .	13	.66
Illinois . . . . .	1,397	7.79	Mississippi . . . . .	24	.64
Iowa . . . . .	458	6.68	Louisiana . . . . .	32	.62
Indiana . . . . .	464	6.49	Delaware . . . . .	3	.59
Nevada . . . . .	21	6.38	Alabama . . . . .	29	.56
Ohio . . . . .	798	5.59	Rhode Island . . . . .	8	.55
Colorado . . . . .	119	5.29	Georgia . . . . .	33	.52
California . . . . .	359	4.45	New Jersey . . . . .	33	.43
Pennsylvania . . . . .	829	4.10	Arkansas . . . . .	17	.40
South Dakota . . . . .	85	4.09	Massachusetts . . . . .	29	.32
Missouri . . . . .	342	3.99	Texas . . . . .	36	.30
Virginia . . . . .	188	3.38	Florida . . . . .	6	.25
Nebraska . . . . .	63	2.14	State not specified . . . . .	186	1.96
Vermont . . . . .	18	2.14			
Tennessee . . . . .	120	1.96	Total . . . . .	11,971	4.35
North Carolina . . . . .	100	1.81			

• **Simple Goiter.**—Out of the 11,971 cases, 4289 were from urban districts and 7682 from rural. The ratios are, respectively, 4.37 and 4.32. In other words, the rural rate is 99 to urban 100. Simple goiter is seen to be somewhat commoner than exophthalmic goiter in rural districts. Also, its ratio of occurrence is much smaller in the large cities than is that of exophthalmic goiter. Thus, for example, for New York City the ratio is 0.76; for Philadelphia, 1.11; for Boston, 0.20; and for Chicago the rate is 11.51. We see, then, that the rate for the great eastern cities is less for simple goiter than for exophthalmic, whereas for Chicago the rate is even greater than for exophthalmic goiter and is more than fifty times as great as for the city of Boston. The distribution of simple goiter in the various states is a good deal like that of exophthalmic goiter, but is even more concentrated in the States of the Northwest and of the Great Lakes. For the Southern States the rate is small and is relatively low as compared with exophthalmic goiter for the densely populated states of Ohio, Pennsylvania and New York. As in the case of exoph-



thalmic, so in the case of simple goiter, the black belt of the South is relatively free from it, whereas the agricultural regions of the North have relatively far more of it than of exophthalmic goiter, and the agricultural section which is occupied by a mixture of foreign and native whites has a much higher rate than that occupied by native whites primarily.

Simple goiter is commoner in the sparsely settled group (13.9) than in any other of the series. It is next commonest in the mountain group (10 per 1000). It is rarest in the maritime group (0.7). It will be recalled that a large part of the sparsely settled group is really a mountain district, so that the large amount of goiter in the mountain regions is in striking contrast with the small amount near the eastern seashore, and this is only in small degree to be accounted for by the fact that the negro population is greater at the seashore and has something less than half the incidence of simple goiter than the white population has.

It is clear that certain European races are characterized by an extraordinary rate of simple goiter. Thus, in the group of sections occupied by 10 per cent of Finns or over, we have a rate of 20.3, but this may be because the Finns occupy mountainous regions. However, the Scandinavian rate is 13.22, and these are mostly agriculturists; but both the Finns and the Scandinavians are found in the Northwest, where there is reason for thinking that the environmental conditions tend to increase the amount of simple goiter. The end result of this complex of causes is, then, the practicable equality that there is between urban and rural districts. On the one hand the rural rate is depressed by the low rate in the agricultural districts of the South, especially those occupied by negroes. On the other hand the rural rate is raised by the high incidence of simple goiter in the great agricultural territories of the North and Central West. The urban rate is raised by the high incidence in Chicago and other cities of the Great Lakes region, but is depressed by the extraordinarily low rate in the great cities on the Atlantic Coast, where those conditions which incite goiter in the Great Lakes region and the Northwest seem to be largely absent.

*Geographical and Racial Distribution of Thyrotoxic Goiter.*—Out of 2,510,791 men examined for military service, this disease was recorded in 8647 men, of which 3684 were from urban districts and 4963 from rural. The ratio for rural districts was 2.80 and for urban 3.76. This gives a proportion of rural to urban of 74 to 100 for this disease. Inquiring into the significance of this defect, we have first to note that it is relatively uncommon in New York City (2.78); in Philadelphia (2.12), and still more in Boston (0.56), whereas it is exceedingly common in Chicago (8.59). It is clear, then, that the high urban rate is not a characteristic of cities as such, but it is due to the presence in certain cities of conditions

especially inciting to this disease or of a population peculiarly liable to it. In comparing the incidence of exophthalmic goiter in the different states, we find there is less of it in the southern states of Texas, Arkansas, Florida, Louisiana, Alabama and Mississippi. These constitute part of the great rural area of the country. On the other hand the more densely populated states of Michigan, Illinois, Pennsylvania and Ohio come toward the top of the list. However, it is clear that it is not density alone that determines the order of the States, since Massachusetts is third from the bottom and Rhode Island and Connecticut are in the lower third of the series. One reason why the Southern States have such a small proportion of exophthalmic goiter is because of the negro population. However, in the black belt the rate for exophthalmic goiter is only 0.99 and even in the South outside of the black belt it is 1.60, while in the northern agricultural districts the ratio is 3.95 and 4.95. Indeed, the eastern manufacturing district has a smaller rate for exophthalmic goiter than have the agricultural districts of the North. But is it not solely due to the absence of a negro population that Wisconsin, Michigan and Oregon stand so high in the series of states with exophthalmic goiter? Examination of the map shows that the whole districts around the Great Lakes and the extreme Northwest are districts of high incidence of exophthalmic goiter, whereas both urban and rural districts in the East are comparatively free from it. We conclude, therefore, that there is something in the conditions of the region referred to which tends to produce exophthalmic goiter. As the end result of all these considerations we see that a deficiency of exophthalmic goiter in the rural population is due to a complex of causes, such as—

(a) A relative insusceptibility of negroes to this disease.

(b) The relatively small incidence of the disease throughout the southern rural states of both whites and blacks.

(c) The relatively high incidence of the great cities of the Great Lakes area, such as Chicago, Cleveland, Detroit and Milwaukee; its frequency throughout the more densely populated states of the Great Lakes Basin, such as Ohio, parts of Pennsylvania and Michigan; and its frequency in cities of the North Pacific States.

The end result, therefore, shows an incidence in rural districts of 74 per cent of urban, the frequency of which is merely the result of these causes acting in different directions.

Exophthalmic goiter has its maximum frequency (6.68) in the Finn group. This is, however, largely because the Finns occupy only the areas where goiter is exceptionally common. Exophthalmic goiter is found also to a large extent among the Scandinavians (5.03) and in the Russian group (4.66). It is commoner in the mountains than at the sea-coast (1.39). Its minimum is in the desert group (0.66). Exophthalmic

goiter is closely associated with simple goiter which finds its maximum of 20.03 among the Finns and a high rate of 13.90 in the sparsely settled, largely mountainous, non-desert areas of the North. The smallest ratios are found among the Mexicans of the South (0.65) and among the French Canadians (0.42). In general the rate for both simple and exophthalmic goiter is higher as we approach the northern tier of states spreading from Lake Huron to the Pacific Ocean. A racial element may be present in its distribution as it is commonest among Finns (20 per 1000) next among Scandinavians (13 per 1000), next among Germans and Scandinavians (10 per 1000), native white North agricultural area (5.3 per 1000), natives of Scotch origin (1.3 per 1000) and French Canadians (0.4 per 1000). It is difficult to say whether the high rate for the Scandinavians is due to the fact that they live almost exclusively in the North, or whether the high rate of goiter in the Northwest is due to the presence of many Scandinavians there. However, the fact that the rate is higher among Finns than among Germans and Austrians who live in the same general area, indicates that the inciting conditions, whatever they are, of the goitrous part of the United States, influence the production of goiter especially in the Scandinavian and Finnish races.

#### ECONOMIC, SOCIAL AND MILITARY SIGNIFICANCE OF ENDEMIC GOITER AND CRETINISM.

In an interesting article on goiter as an economic loss, Dr. Oswald writes: "If we allow the military statistics of Switzerland to speak for themselves, we shall see that an average of 1700 recruits, *i. e.*, 7 per cent, are annually pronounced unfit for military service because of goiter, and 400 drilled soldiers, *i. e.*, 2 per 1000, are annually discharged from the service because of the same malady. Because of idiocy, 180 conscripts are annually rejected. The medical conception of idiocy includes many conditions, but it is certainly not too much to attribute half of this number to cretinism, which gives us the figure of 90. Eighty recruits are annually rejected on account of deaf-mutism, two-thirds of which number must be considered as due to cretinoid conditions, and this gives us the number of 52 to be included in our calculations. Because of insufficient stature, 1900 recruits are annually rejected from military service, of which number at least one-half must be attributed to the cretinoid degeneration, so we again have the number of 950. By adding these figures together, we obtain the very considerable total of 3000 recruits annually rejected because of the goiter endemic, and should we continue our calculations through the ten years of Swiss military duty, we come to the enormous figure of 30,000, or nearly one-fourth of the Swiss Army." Bircher calculates the loss to the Swiss army due

GOITER EXOPHTHALMIC.

Groups.	Total cases.	Ratio per 1,000	Ratio per 1,000 cases in groups.	Groups.	Total cases.	Ratio per 1,000	Ratio per 1,000 cases in groups.
Agricultural, native white, North, 73 per cent plus	797	3.95	7.46	Mountain whites . . . .	281	3.86	6.80
Agricultural, foreign and native white . . . .	1,451	4.95	9.40	Indian, sparsely settled .	42	1.32	2.49
Agricultural, native white, South . . . . .	686	1.60	3.09	Mexican, sparsely settled	17	.61	1.30
Agricultural, negro, 45 per cent plus . . . . .	179	.99	1.80	Native white, Scotch origin	83	1.53	3.23
Eastern manufacturing .	508	2.28	3.83	Russian, 10 per cent plus	177	4.66	7.87
Communers . . . . .	173	2.33	4.33	Scandinavian, 10 per cent	790	5.03	9.26
Mining . . . . .	297	3.10	5.46	Finns, 10 per cent . . .	91	6.68	12.85
Sparsely settled, 3 or less per square mile . . .	119	2.63	4.60	French Canadians, 10 per cent plus . . . . .	70	.76	1.11
Desert . . . . .	8	.66	.99	German and Scandinavian, each 10 per cent plus .	458	4.64	8.97
Maritime . . . . .	28	1.39	2.03	German and Austrian, 20 per cent plus . . . . .	410	4.13	8.07
Mountain . . . . .	246	4.67	8.16	German and Austrian, 15 per cent plus . . . . .	1,539	4.38	8.11

GOITER, SIMPLE.

Groups.	Total cases.	Ratio per 1,000	Ratio per 1,000 cases in groups.	Groups.	Total cases.	Ratio per 1,000	Ratio per 1,000 cases in groups.
Agricultural, native white, North, 73 per cent plus	1,069	5.29	10.00	Mountain whites . . . .	258	3.54	6.24
Agricultural, foreign and native white . . . .	2,039	6.96	13.21	Indian, sparsely settled .	37	1.16	2.19
Agricultural, native white, South . . . . .	757	1.76	3.41	Mexican, sparsely settled	18	.65	1.38
Agricultural, negro, 45 per cent plus . . . . .	138	.77	1.39	Native white, Scotch origin	71	1.31	2.77
Eastern manufacturing .	418	1.87	3.15	Russian, 10 per cent plus	210	5.52	9.34
Commuters . . . . .	126	1.70	3.16	Scandinavian, 10 per cent	2,075	13.22	24.33
Mining . . . . .	906	9.47	16.65	Finns, 10 per cent . . .	273	20.03	38.56
Sparsely settled, 3 or less per square mile . . .	628	13.90	24.25	French Canadians, 10 per cent plus . . . . .	39	.42	.62
Desert . . . . .	36	2.98	4.45	German and Scandinavian, each 10 per cent plus .	988	10.02	19.36
Maritime . . . . .	14	.70	1.02	German and Austrian, 20 per cent plus . . . . .	638	6.42	12.56
Mountain . . . . .	529	10.03	17.55	German and Austrian, 15 per cent plus . . . . .	2,208	6.28	11.64

TOTAL GOITER.

Groups.	Total cases.	Ratio per 1,000.	Ratio per 1,000 cases in groups.	Groups.	Total cases.	Ratio per 1,000.	Ratio per 1,000 cases in groups.
Agricultural, native white, North, 73 per cent plus	1,866	9.24	17.46	Mountain whites . . . .	539	7.40	13.04
Agricultural, foreign and native white . . . .	3,490	11.91	22.61	Indian, sparsely settled .	79	2.48	4.68
Agricultural, native white, South . . . . .	1,443	3.36	6.50	Mexican, sparsely settled	35	1.26	2.68
Agricultural, negro, 45 per cent plus . . . . .	317	1.76	3.19	Native white, Scotch origin	154	2.84	6.00
Eastern manufacturing .	926	4.15	6.98	Russian, 10 per cent plus	387	10.18	17.21
Commuters . . . . .	299	4.03	7.49	Scandinavian, 10 per cent	2,865	18.25	33.59
Mining . . . . .	1,203	12.57	22.11	Finns, 10 per cent . . .	364	26.71	51.41
Sparsely settled, 3 or less per square mile . . .	747	16.53	28.85	French Canadians, 10 per cent plus . . . . .	109	1.18	1.73
Desert . . . . .	44	3.64	5.44	German and Scandinavian, each 10 per cent plus .	1,446	14.66	28.33
Maritime . . . . .	42	2.09	3.05	German and Austrian, 20 per cent plus . . . . .	1,048	10.55	20.63
Mountain . . . . .	775	14.70	25.71	German and Austrian, 15 per cent plus . . . . .	3,747	10.66	19.75



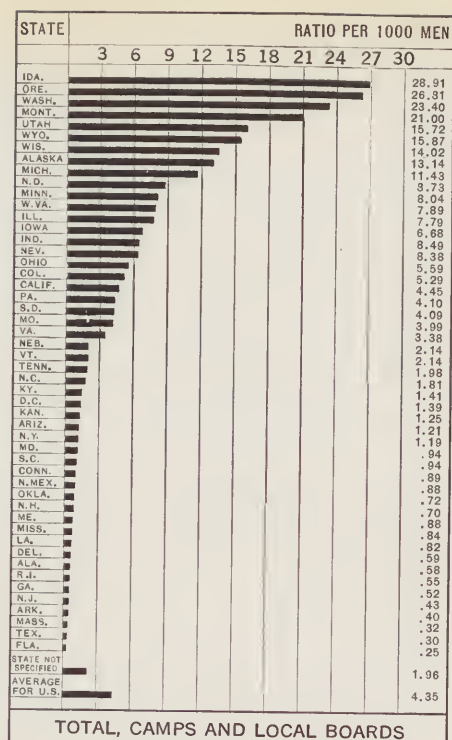
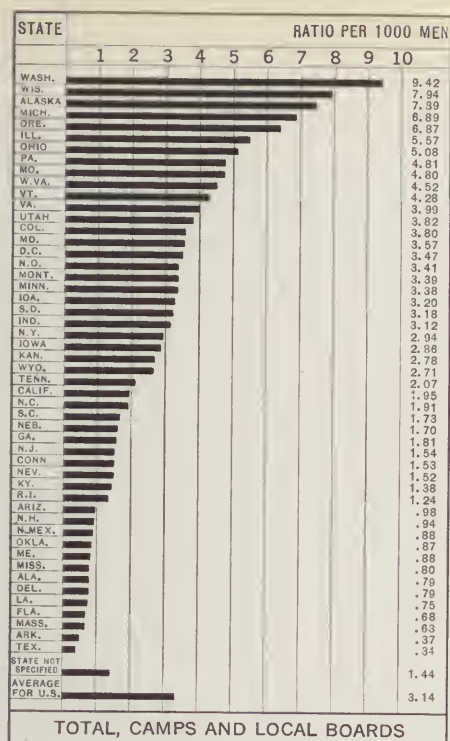


FIG. 60.—Defects found in 2,510,596 drafted men examined.

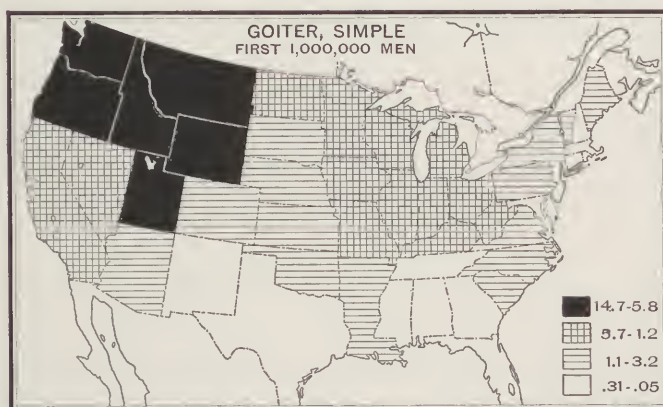


FIG. 61.—Map of the United States showing by States the varying incidence of simple goiter as found at mobilization camps in the first million men; in four grades.

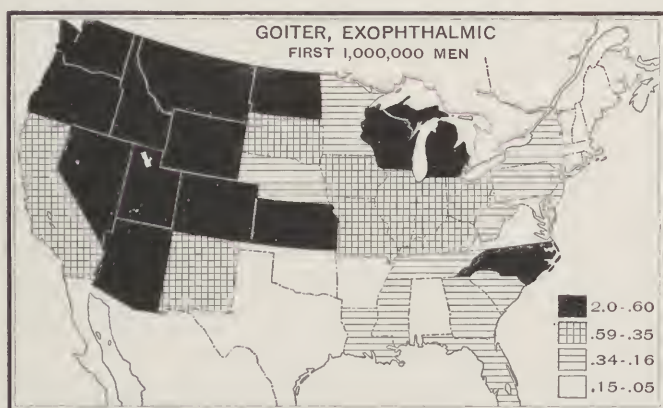


FIG. 62.—Map of United States showing by States the varying incidence of exophthalmic goiter as found in mobilization camps in the first four million men, four grades.

to the goiter endemic at one-sixth of its total force. In France, out of a total of 300,000 recruits, 1200 are annually rejected because of goiter. In Italy 3 per cent of the conscripts were rejected from military service between the years 1859-1864 because of goiter and cretinism.

It is self-evident that these figures have an economic as well as a military significance. It is hardly necessary to mention that cretins, the feeble-minded, the deaf and dumb, become in one way or another a burden upon society. Although the demands which military service make upon the capacity for work are, of course, greater than in the ordinary occupations of civil life, there are many large industries which, on general principles, do not employ young men who have been rejected from military service, and while young men of this class may be for a time unhindered in their callings, they are often ultimately obliged to seek an easier occupation because of infirmities due either directly or indirectly to their goiters.

In these figures women have not been taken into consideration, and they are, as we know, more severely affected than men by the endemism. Baillarger has estimated that in France the relative proportions as to sex incidence are approximately 2 : 5, but where the endemic is intense, the number of goitrous men more nearly approaches that of the women.

The main bulk of the population is not included in these calculations, but although it is impossible to secure such comprehensive and reliable statistics for the entire population, these military statistics are sufficiently illuminating as to the enormous drain upon the defensive and economic resources of certain countries.

### GOITER EPIDEMICS.

Goiter epidemics usually occur in endemic territory, or at least in regions where sporadic goiter is not rare, and are most frequently observed in groups of young people, newcomers to the goitrous locality. These epidemics have been occasionally observed in barracks, boarding schools, seminaries, prisons or other agglomerations of individuals living in crowded space, and do not affect, as a rule, the general population.

The first in date of these epidemics was noticed by Forster, ship's surgeon with Capt. Cook in 1772. While the ship was floating among icebergs, the crew collected pieces of the ice and melted them for drinking purposes. The exterior only was salty, and when this had been melted away, the water obtained was sweet and palatable, and evidently of fresh-water origin. All of the crew who drank of this water suffered from swelling of the thyroid gland, but those who refrained from using it were not affected. Since this epidemic occurred in midocean, St. Lager thinks it cannot be associated with endemic goiter, whereas,

Bircher argues that the ice, having been of fresh-water derivation, was probably formed in some goitriferous river. As it is a well-known fact that microorganisms resist the low temperature of ice, he considers that the Cook epidemic belongs in the endemic class. Repin, on the contrary, thinks that this case has no connection with endemic goiter and is to be considered as a congestion, "a frigore," such as appears suddenly among soldiers after drinking glacier water. In my judgment, both suppositions, the one of Bircher and the one of Répin, may be correct.

Meyer-Ahrens reports an epidemic occurring in a military school in Kronstadt (Siebenburgen) in 1784. Of the 38 pupils, 36 became goitrous in a short time, and 2 of the 7 adults in the institution acquired goiters. The drinking water could not be incriminated as it was the purest in Kronstadt, and was used outside of the institution without deleterious results. Investigations were therefore made as to the hygienic conditions within the buildings, and as a result the rooms were found to be small, badly ventilated, and overcrowded. With a change of quarters and an amelioration of these conditions, the epidemic disappeared.

Another epidemic is reported by Valentin and cited by Ewald and H. and E. Bircher. Early in the year 1783 an infantry regiment was transferred to Nancy, where the endemicity is slight. During the winter of the same year, which was remarkable for its sudden changes of temperature and general bad weather, 38 men of this regiment acquired goiter; in 1785, 205 men became goitrous; in 1786 there were 425 cases; in 1787 the number of cases had diminished to 257; in 1788 to 132; and in 1789 the epidemic terminated with 43 cases. It is especially noteworthy that in this epidemic only the common soldiers were attacked, the officers, corporals and sergeants remaining exempt from the disease, although living in the same barracks and making use of the same drinking water. This exemption has been attributed to the fact that the officers and non-commissioned men drank wine, while the common soldiers were obliged to satisfy their thirst with water. As my observations have not convinced me that the common soldier is more addicted to drinking water than his superior officer, this theory does not seem to me conclusive. Taussig thinks the explanation of this immunity is to be sought rather in the more isolated lodgings of the officers and their less frequent and close contact with the soldiers suffering from the epidemic. He regards this case as evidence in favor of the infection by contact theory, of which he and Kutschera are adherents.

The epidemic which occurred in the fortress of Silberberg in Silesia during 1819 has been given a detailed and still interesting description by the regimental surgeon, Haneke. Goiter is still endemic in the town of Silberberg (Eulengebirge), and even at that time the drinking water



was regarded as the principal etiological factor. Haneke states that the recruits were drawn from immune territory, and that after scarcely three weeks' residence in the fortress, many of the young soldiers complained of oppression and shortness of breath in mountain climbing. Examination of these men showed the thyroid gland to be swollen, but still soft. As they were otherwise in good health, Haneke recommended that they be permitted to perform their service with open collars. The number of those affected augmented so rapidly that early in 1820 some 20 odd were admitted to the hospital, the thyroid gland having acquired such volume that, even with open collars, it had become impossible on account of dyspnea for the soldiers to perform their military service. During the following summer the development of the disease was slow, but in the ensuing autumn, which was exceedingly damp, cold and stormy, the epidemic rapidly assumed such proportions that out of the 380 composing the battalion, 60 had been reported goitrous by November 17, and on November 20, three days later, this number had increased to 100 and augmented steadily until December, when only 70 of the battalion were exempt. Haneke further states that those individuals who used only boiled water very rarely showed any swelling of the thyroid gland, and that where a slight enlargement occurred, it never developed into a real goiter. Eventually the epidemic became so severe that the battalion was transferred to Schweidnitz where, within a short time after removal from the goitrigenous influences, the condition of the men improved and all traces of the goiters acquired in Silberberg disappeared, except in those cases where chronic changes had ensued.

In citing this epidemic, Schittenhelm and Weichardt remark that "Young adolescent recruits from the Polish plains were subjected to those intensely goitrigenous influences," and they furthermore add, "It is peculiarly significant for our conception of the etiology of goiter that these young people, belonging to a population totally exempt from the endemism, should be so acutely and subacutely affected by the disease."

Epidemics were observed in 1859-61-63 in Colmar when different regiments were successively attacked, first the cuirassiers, then the infantry and cavalry. Epidemics occurred repeatedly in the barracks of Briançon during 1812, 1819, 1826, 1841, 1842, 1850, 1857, 1860 and 1863. These have been reported by Collin.

Fodéré observed goiter epidemics in Strassburg and says that soldiers in garrison there seldom escape goiter. He also saw an epidemic in the Collegium of Strassburg during which over one-third of the students developed goiter. According to Sigand, goiter suddenly developed among the Brazilian recruits of the Rio Urubez (Goyaz) with such severity that the recruits were seized with panic and deserted to their



own homes in the Province of Para, where their goiters rapidly disappeared. Urubez is known as an endemic center.

In Neu Breisach between the years 1847-71 five epidemics are reported, during the last of which, in an infantry regiment of 1002 men, there were 647 cases of goiter.

In the year 1877, during an epidemic in Belfort, 900 of the 5300 men in the garrison became goitrous. Seidlitz reports an epidemic which occurred in 1877, when the Russian troops, during the war with Turkestan, occupied the city of Kokan; of the 2753 men, 245 became ill with goiter and the condition of the troops became so alarming that they were transferred to the neighboring city of Margelan, where a satisfactory amelioration immediately ensued.

Hesse observed a goiter epidemic in the school of non-commissioned officers in Marienberg, Bavaria. The pupils were from 14 to 17 years of age, and the epidemic was attributed to the tight coat collars, this portion of the uniform often becoming too small because of the rapid physical development due to the youthful age of the pupils. Goiter is not rare in the population of Marienberg.

In Clermont-Ferrand an epidemic is reported as occurring in 1812 in the local seminary when 50 of the students developed goiters within a short time. Several epidemics of goiter occurred in the barracks of Clermont-Ferrand between 1843 and 1860. In 1889 Augieras observed in Clermont-Ferrand two peculiarly localized foci—one in the wing of a pavilion, and the other in the third floor of a barracks. More recent epidemics are reported by Costa in Drome, by Caljage in Finland, occurring in an otherwise goiter-free territory. Cantemessa in Northern Italy reports an epidemic in a military camp, and asserts that such epidemics not infrequently occur among soldiers without being attributable to drinking water or to soil formation. Cantemessa attributes these epidemics to infectious conditions due to extreme summer-heat, great fatigue and lack of hygiene.

Bottini observed an epidemic in the prison of Pallanza when, because of reconstruction of one of the wings of the building, the prisoners were crowded together in the remaining part of the prison; after cessation of this temporary overcrowding the epidemic disappeared.

Numerous goiter epidemics have been reported in boarding schools and educational institutions in Lausanne, in Stuttgart, etc., and in the Bishop Cotton School in Simla, India. Kutschera reports an epidemic in the school-house in Göss (endemic territory). The headmaster, his wife and six children, all having come from a goiter-free locality, acquired goiters within two years after occupying an apartment in the school-house. In 1907, 60 per cent of the children of the school were goitrous.

E. Bircher cites an interesting observation made by Cardinal Billiet

in the Normal School at Albertville. From 1840 to 1860 a girls' school occupied the buildings and goiter was unknown. In 1860 architectural alterations were made, and the rubbish from the construction was thrown around the well. The buildings then passed into the possession of the Normal School and within a short time from 25 to 30 per cent of the pupils became goitrous. Upon replacing the well-water by rain-water for drinking purposes, this epidemic entirely disappeared.

The difference between epidemic and endemic goiter is quantitative rather than qualitative, the same conditions and deleterious influences being the cause of both. The fact that epidemics usually occur under overcrowded living conditions where the air space is inadequate, has led McCarrison to suggest that, "Under these circumstances the thyroid gland, which is intimately concerned with the gaseous exchanges of the body, may be abnormally taxed, and the addition of goitrous influences may, by making a further demand upon its functional activity, result in some cases in its visible enlargement." Personally, I am rather inclined to believe that overcrowding increases the chances for infection.

These epidemics in most cases show the same seasonal fluctuation or tendency to increase during the summer season as the endemic disease, hence the name "estival goiter" or "summer goiter." There seems to be no doubt that the conditions for the development of goiter are more favorable during the summer months. Nevet says that the goiter curve in Central Europe reaches its maximum during the months of May and June and McNamara writes of Himalayan India, "It is during and after the rains that the disease most commonly begins and most rapidly develops." This seasonal recrudescence bears some analogy to typhoid fever and to other infectious diseases, and might indicate pollution of the water supply as an etiological factor. Some authors attribute this increased intensity of the disease during the warmer months to the greater quantity of drinking water consumed.

#### FLUCTUATIONS OF ENDEMIC GOITER.

One of the most interesting manifestations of this enigmatical disease is the fluctuation in intensity to which it is subject. Whenever the course of goiter and cretinism has been studied over a long period of time, it has been observed that the disease fluctuates, sometimes alternately increasing and declining, sometimes diminishing persistently until it ultimately disappears. Or the disease may augment in severity in localities where the endemism has been mild, and even make its appearance where it was formerly unknown. Again, the epidemic may disappear almost entirely, persisting only as isolated cases, which are then called "sporadic." If in the latter localities epidemics of goiter occur,

they are usually not attributed to the slight persistent endemicity to which they are really due, but are considered as of sporadic origin. The goitrigenous agent seems to be in abeyance rather than absent, and is apt to attack susceptible newcomers, especially if living under unhygienic conditions, or if crowded into buildings and sleeping rooms with inadequate air space, as soldiers in barracks, or children in boarding schools and students in seminaries.

James Berry has truthfully said that, "Most goiters may be considered as belonging to the endemic class, but the endemicity is so widely spread over the whole country, while at the same time it is so slight that it escapes notice, and cases of goiter are often considered as sporadic which should more correctly be classed as endemic." Baillarger, who studied the question in 60 departments of France, proved conclusively that between the years 1830-1865 the endemic had increased in 26 departments, had diminished in 17, and had remained stationary in the rest. Fifteen of the 17 departments in which he found goiter diminishing were formerly among the most goitrous of the whole of France. In 1880 Kocher noticed a considerable augmentation of goiter in certain parts of Germany and particularly in the neighborhood of Berlin (Berard). The endemism has decreased in some parts of Switzerland, in the Pyrenees, in the Rhinelands, in the Harz Mountains, in Franconia and in Thuringia.

Goiter and cretinism have disappeared from the Island of Niederwörth near Coblenz on the Rhine, where the endemism was formerly so intense that few, if any, of the inhabitants escaped goiter or some of its sequelæ. According to statistics made by Cavatorti in 1907, goiter has completely disappeared in the Italian provinces of Ferrara, Bara, and some districts of Sicily. It has appreciably diminished in Northern Italy, which was formerly the principal center of endemicity in the peninsula. In certain valleys of Spain (Granada) goiter was unknown until the early part of the last century, when it first appeared and spread rapidly over a wide area. In South America, at Mariquita, and on the plateau of Bogota, the number of goiters declined during the eighteenth, and increased again in the nineteenth century.

McCarrison cites an interesting example of the appearance of goiter in a locality previously exempt. In the hill state of Nagar goiter was unknown, according to the testimony of the ruling chief and principal dignitaries, until the year 1898-99, when 4 goitrous individuals came to reside in the village of Nagar. Three of these individuals were members of a priest's family and lived in a house close to the head of a spring supplying the village with drinking water. Six years later McCarrison examined the inhabitants of Nagar for goiter and found in the priest's family 7 goitrous individuals, 3 being the imported cases, while four children had developed the disease in Nagar. Since the arrival of the

original 4 imported cases of goiter, 18 cases developed in the village itself, of which 17 were in children under 16 years of age. All these 18 cases came from a part of the village supplied by the spring at the head of which lived the priest's family.

Two years subsequently McCarrison again examined the inhabitants of the village of Nagar and found 13 new cases, of which 11 were in children. The malady did not spread in any definite line nor were all of the children in the same house always affected.

In certain districts of Brazil (Natividade, Rio Grande del Sul) goiter made its first appearance about 1830.

Attention is drawn to the etiological value of these observations by Ewald, who says, "As these observations have been authenticated by reliable investigators, and are, moreover, of so simple a nature that error is almost excluded, they acquire great importance for the etiology of goiter, as they show that the primary cause of the disease cannot be a permanent and unchanging condition inherent in the locality concerned, but must be sought, partially at least, in such conditions as are subject to fluctuation, sometimes augmenting and sometimes declining."

The course of development of goiter itself is fluctuating in the incipient stage. A newcomer to a goitrous locality may acquire an enlargement of the thyroid gland in a length of time varying from eight days to three months. This is especially true of foreign travelers who come to spend the summer months in regions where goiter is endemic. Often this swelling augments rapidly for a time and then recedes more or less completely. Now, unless the patient is removed from the goitrogenous influences, the swelling will eventually fluctuate in size and increase, but not uniformly, sometimes growing with the seasonal recrudescence of the goiter causative factor, sometimes augmenting during infectious diseases or through some other cause. Incipient goiter usually disappears spontaneously when the patient leaves the endemic territory, but if again subjected to these deleterious influences, hyperplasia of the thyroid gland will again ensue, and with every renewed recurrence the gland remains larger than before, until a chronic degenerative process results.

#### FLUCTUATIONS OF CRETINISM.

Endemic cretinism is subject to the same fluctuations as goiter. Ewald states that in the German Black Forest, in the Weserthal, in Feldberg, and in the neighborhood of Homberg, cretinism has died out, although there has been no change in the water supply of these places.

This is also true of Freiburg in Breisgau and other localities where cretinism has disappeared, and where the water supply remained the same. Roesch, writing in the first half of the 19th century, counts



4967 cretins in Württemberg, and mentions districts where formerly there was little or no cretinism, but where at the time of his writing many cretins were to be found. Among the places mentioned by Roesch are Ergenzingen, where in 1807 cretinism was unknown, while in 1847 there were 26 cretins. In Beinstein and Knittlingen cretinism had diminished, while in Offenau and Schuttringen it had augmented. In Vachingen, Stockheim and Brachenheim, endemic cretinism had declined and in Güglingen it had alarmingly increased, etc. In Alt Oberndorf, where formerly there were no deaf-mutes or idiotic individuals, Roesch counted 36 cretins.

At the present time cretinism has diminished throughout Württemberg.

Kutschera reports concerning the fluctuation of cretinism in Styria as follows: in 1861 in a population of 978,785 there were 5856 cretins, *i. e.*, 1 cretin to 167 inhabitants; at the present time there are 2517 cretins, or 1 to every 539 inhabitants.

Graz and the district of Maria Zell, where formerly cretinism prevailed, are now free from the cretinoid degeneration. Formerly in the district of Oberwölz there was 1 cretin to 24 inhabitants, and the district of St. Gallen was without cretinism. These conditions are now reversed. The district of Oberwölz is now cretin-free, but in the district of St. Gallen cretinism is widely distributed. In the district of Neu-markt, where endemic cretinism was formerly intense, it has diminished remarkably, whereas in the districts of Oberzeiring and Judenburg it has greatly increased.

In the Paltental endemic cretinism has disappeared from many places and remained stationary in others.

Not only does the disease fluctuate in endemic area, but the degree of endemicity also varies greatly between different adjacent villages and even in different parts of the same village. St. Lager tells of the village Antignano (Asti) which drew its water supply from three wells. The families using the first well suffer from both goiter and cretinism, those using the second are only goitrous, and those who drink water from the third well are entirely free from both diseases.

Kutschera mentions the village of Lassing in the district of Liezen, consisting of five peasant houses, all of which had the same water supply and where the conditions of life were identical, yet in one of these houses there were many cases of cretinism, while the inhabitants of the other houses remained exempt.

McNamara states that, "In villages situated along the banks of the Ravi which are subject to the same telluric, atmospheric and hygienic conditions, the difference in the endemicity of goiter in villages quite close together was remarkable."

Bircher reports that cretins and deaf-mutes are numerous on the right bank of the River Aare, while the left bank is completely free from cretinism.

**Conclusions Drawn from the Study of the Fluctuations of Goiter and Cretinism.**—On the whole endemic goiter seems to be diminishing intensively if not extensively. The large, degenerated goiters, often accompanied by myxedematous complications, which were formerly frequently encountered in endemic centers, are rarely seen now, and there can be no doubt that the cretinoid degeneration has sensibly decreased both in frequency and in area of distribution. It seems probable, after examining all the statistics before us, that the total number of goiter-bearers has not greatly altered, but that these goiters remain small, that their symptoms are less severe, and that their dread sequelæ of cretinism and deaf-mutism occur less frequently.

This decline in the severity of the manifestation of the disease is probably due to several factors such as the general increase in well-being, improved hygienic conditions, and to the fact that the population is no longer a fixed and unchanging product of the endemic locality as formerly.

Under modern conditions of life the peasant frequently emigrates or moves to the city, and his place is taken by a newcomer often from immune territory, so that opportunity for the accumulated toxic effect of the goiter poison upon successive generations is far less frequent than of old.

Nor must it be forgotten that the surgical treatment of goiter has done much toward preventing the monstrous deformities which were formerly so familiar a sight in regions of severe endemicity.

At present, when a goiter commences to assume such proportions as to cause inconvenience or disfigurement, the case is given medical treatment, and if this fails to arrest the development of the disease, recourse is had to surgical intervention, from which the best and most permanent cures known to us have been obtained.

#### GOITER IN ANIMALS.

As we have already seen, animals in endemic territory suffer from goiter as well as man. Vegetius (4th century) observed goiter in draft animals, and mentions struma as well as swellings of the parotid gland and scrofulous tumors in his "*Ars Veterinaria sive Mulomedicina*"—"Plerumque strumæ, vel parotides, aut scrophulæ jumentorum guttur infestant et faucium tumorem producunt." Classic writers report lions as goitrous in a certain portion of the Mediterranean Coast, in the Atlas Mountains, where the existence of the endemism was recognized

by the ancients. The Berber traveler, Leo Africanus, wrote of the lions of Morocco in the latter part of the 15th century, that they were both goitrous and cowardly, a statement which explains the old proverb, "Thou art brave as a lion of Agla, whose tail may be eaten by calves." In modern times observations and investigations concerning goiter among animals have become more and more frequent with the growing realization that the factors responsible for the degenerative process in man occasion similar results in the animal kingdom. I am now speaking of endemic influences upon animals under natural conditions. Later I shall refer to the valuable experimental work upon animals to which we owe much of the little knowledge we possess on this subject. Goitrous dogs and pigs were observed by Kaissler in the Valley of Aosta, and by Fodéré in the Maurienne, while Rougieux and Tallard observed them in the Department of Meurthe, Verdel in the Canton of Vaud, Schneider in the Canton of Berne, Roesch in Württemberg, Guerdan in the Grand-Duchy of Baden, and Mollien in New Granada (Columbia). Campbell and Bramley report the finding of goitrous dogs on the slopes of the Himalayas, and McClelland saw goitrous dogs and cats on the banks of the Gunduk, a tributary of the Ganges.

Goiter has been found among cattle and sheep in the Auvergne, in the Jura, in Switzerland, in Baden, in Württemberg, in the Danube Valley, in Piedmont, in Siberia, and in Brazil. In the valley of the Gunduk, where McClelland found goitrous dogs and cats, Campbell observed this disease among sheep and goats. Bramley saw goiter among camels in Purneah. An observation of Gustave Radde's, which Bircher cites,<sup>1</sup> is especially interesting, as it shows that goiter exists in wild animals as well as among their domesticated brothers. In the district of Nertschinsk, in Siberia near the Chinese frontier, Radde encountered a goitrous antelope which he called "antelope gutturosa." South of the Baikal-Sea he did not find this goitrous species, and it is exceedingly probable that what he considered a natural species of antelope was merely a pathological product, since in the region inhabited by these animals endemic goiter prevails, while it is absent south of the Baikal-Sea.

Russian physicians have observed goiter among horses in the same regions of Siberia where Radde found the goitrous antelope, and also in the Government of Olonetz. It occurs among horses in Guatemala, in the United States, in Brazil, in the Argentine Republic, in Carinthia, in the Valley of Aosta, in the Department of Meurthe, and, according to Mayor and Vicat, in the Canton of Geneva.

Baillarger reports the frequent finding of goiter among mules in the

<sup>1</sup> The greater part of these preceding observations concerning animals is cited from H. Bircher.

Maurienne and Modena; in the latter locality he found 19 goitrous mules in a stable of 20; while Peronnet and Lecoq saw in Savoy 28 goitrous mules among 60, and among 45 horses 15 had goiters. Pellat in Allevard near Grenoble reports that out of 55 mules examined by him 47 had goiters. According to Baillarger, in the stables of the gendarmerie at St. Jean du Maurienne 4 out of 7 horses became goitrous within less than two years. Raynard and Rougieux maintain that they have observed a decline of intelligence in horses and dogs suffering from goiter. We have already mentioned Marine's report of the wide dissemination of goiter among animals along the Great Lakes of North America. He affirms that 90 per cent of the street dogs of Cleveland show some degree of hyperplasia of the thyroid gland, and in some cases actual colloid goiter. He considers this hyperplasia as an indubitable indication of endemism. In well-cared-for dogs there is a lesser degree of the thyroid hyperplasia. Marine further finds that 90 per cent of the sheep on Lake Erie show some enlargement of the thyroid gland and that the cattle are affected in a lesser degree. He records that in Michigan twenty years ago the sheep industry suffered a set-back on account of the number of cretin lambs born, but today this condition is gradually disappearing owing to acclimatization, or perhaps to the development of a natural resistance to the disease, but especially to the use of iodine-containing salt. Marine reports the occurrence of goiter among fish in endemic localities and says that carnivorous fish only are affected under natural conditions. Artificially bred trout are peculiarly liable to this disease. Gaylord, of Buffalo, has made very interesting observations concerning goiter epidemics among fish. The fish tanks that he described were located one above the other and fed from the same stream flowing from one tank into the next, from above downward. In the first tank the fish were 3 per cent goitrous; in the second, 8 per cent; in the third, 45 per cent; and in the fourth, 85 per cent.

In the stream above the tanks the transplanted fish remained healthy, from which circumstance Plehn draws the conclusion that the noxious agent is not contained in the water, but in the bed of the tank whence it passes down the stream in accumulating quantities. Kutschera considers that these observations clearly prove that the goiter agent is not conveyed by the water itself, but that it is transmitted by contact in the water. If that is the case, it is difficult to understand why the fish in the stream below the tanks should escape the infection, as is reported by Marine and Lenhardt farther on in the present treatise.

The similarity of fish-goiter with that of warm-blooded animals is not only histologically established, but is also further confirmed by Gaylord's experiment in giving dogs and rats water to drink from these goiter tanks, when as a result they frequently developed an enlargement of the thyroid gland.



Another observation of Gaylord would seem to speak in favor of the parasitic origin of goiter. Upon the addition of an infinitesimal quantity of antiseptic, such as sublimate or potassium iodide (solution of 1.5 millionths), to the tanks a slow but unmistakable retrogression in the fish-goiter occurred. When the goitrous fish were transferred into different waters the goiter disappeared, and even in the infected tanks, some trout recovered spontaneously and developed complete immunity to the injurious influence of the goiter agent.

The following observations of Drs. Marine and Lenhardt were made in a private hatchery in the mountains of Pennsylvania during the months of October and November, 1909. The fish tanks in question were arranged in a single series down the course of the brook, each house containing several tanks. A single spring supplied the six upper houses, while the lower five received the water that had passed through the upper six, together with that from a second small spring, and a six-inch pipe line from a large stream about a quarter of a mile to the left. Between houses 6 and 7 the water followed the original brook for a quarter of a mile, then it was again collected by means of a dam and entered the lower division commencing with house 7, with the addition to its volume above mentioned, otherwise the water was carried in covered race-ways made of lumber. As a result of the examination of the fish contained in these different tanks and houses and in the race-ways above and below all houses, the authors conclude that: "Fish from the race-way above all houses, and which have never been confined to the tanks, maintain normal thyroids throughout their lives, but beginning with the uppermost tank the fish are markedly affected and there is a gradual increase in the degree of thyroid proliferation which reaches its maximum in house 6, the last of the upper series. Beginning with house 7 there is a marked improvement and lessening of the active thyroid proliferation coincident with the greatly increased water supply and the probable purification of the water in its passage from house 6 to 7 along the original bed of the brook." The examination of the fish from the tail-race, living wild but in the polluted water, showed their thyroids to be normal in type. Examination of the older fish that were removed from the tanks into the larger stream indicated that, although the thyroid tissue had invaded all the structures beneath the pharyngeal mucosa at some past period of their lives, nevertheless, their stay of from five to six months in a natural environment afforded a complete relief, so that the thyroids resumed their resting or colloid state. The authors conclude that "overfeeding or overcrowding, and a limited supply of water produce filthy unhygienic tanks, and such tanks are in a very important but still unknown way associated with thyroid hyperplasia."

It is interesting to note that trout also conform to that striking

characteristic of endemic goiter, viz., the capacity for spontaneous recovery on removal from the infected area. The markedly place-character of the disease even in the case of these fish is thus illustrated (McCarrison).

That goiter can develop in fish from marine waters is well illustrated by the cases reported by Cameron and Vincent, and by Marsh and von Willer, in 1918. The two first authors observed a well-developed goiter in a small shark of the genus *squalus* off the Pacific Coast of North America. Marsh and von Willer observed 5 cases in the sea bass (*serranus*). One specimen was plainly colloid goiter, while, another one was microscopically a step in advance toward epithelial increase of large alveolar type and shrinkage of the colloid content. In another, cellular hyperplasia was predominant, the colloid being much diminished. In another case marked regression was present. None of them presented signs of malignancy.

Nevertheless, as a whole, goiter and cretinism are less frequent in animals than in human beings, and it should not be forgotten in forming conclusions based upon animal experiments, that animals possess a greater degree of resistance to the goiter agent than exists in man. Animals may remain immune from goiter in the regions where the endemism prevails among human beings. The domestic water-drinking animals are much more subject to goiter than those which obtain their provision of water from green food. Thus, it is extremely difficult to produce goiter experimentally, for example, in rabbits, guinea-pigs and monkeys.

McCarrison reports from the districts of Chitral and Gilgit in the Western Himalayas, where the endemicity is most intense, that among 567 animals examined by him he did not encounter one case of the disease. In one village where 45 per cent of the male population were goitrous, he examined all the dogs without finding a single animal that showed enlargement of the thyroid gland. This is in direct opposition to the observations of Adam, whose notes upon endemic goiter among animals in the territory of Augsburg and along the River Lech show that these endemic goiters are coincident with the malady among human beings, the endemic area for human beings and animals alike being confined to the left bank of the river.

Adam reports a goiter epidemic observed by him among horses in Augsburg. In certain stables in the east and northeast portions of Augsburg, newly imported horses from immune territory acquired a swelling of the thyroid gland which receded upon the application of iodine. All of these stables lay upon the left bank of the River Lech, while horses stabled in the west side of the city did not suffer from goiter. Adam further states that not all the horses in the affected stables acquired goiter, about one-half of each new lot remaining exempt, so that a cer-

tain predisposition must exist among them as among human beings. Adam cites the observation of the veterinary surgeon, Mussgnug, that in the whole territory of Augsburg goiter prevails among animals on the left side of the River Lech and not on the right side.

Adam further observes that among very young dogs marked swelling of the thyroid gland is frequently observed, but that this goiter usually disappears as the dog acquires its growth.

Schittenhelm and Weichardt remark that this coincides with the predominance of thyroid enlargements among children in endemic territory which, according to Kocher, attains 90 per cent, reaching its maximum at about the tenth year, and then retrogressing. Berard cites an observation reported to him by Dr. Furet, of Brides, who brought a bitch from Geneva to Brides, where the animal acquired goiter. The following year she gave birth to several puppies, one of which was born with a thyroid tumor. This goitrous puppy was seriously retarded in his development; he was very slow in learning to eat alone, did not understand when called, and finally allowed himself to be run over and killed by a wagon of which the horse was advancing at a walk.

It is interesting to observe that in endemic goiter among animals the influence of individual predisposition, sex and hygienic living seems to be the same as in man. In groups of animals under precisely the same conditions and exposed to the same toxic influences some will develop goiter and others will remain immune, as is clearly demonstrated in all of the endemics occurring among horses and mules in certain stables.

Goiter occurs more frequently in the female sex among animals, just as is the case in human beings, and this disparity decreases in proportion as the endemic increases in intensity. And, furthermore, from Marine's observation that goiter is less frequent among well-cared-for dogs than among neglected ones, it would seem that general well-being augments the individual power of resistance in animals as in man to the endemic process.

### THEORIES REGARDING THE ETIOLOGY OF GOITER.

The various theories as to the etiology of goiter may be divided into two groups:

1. That of the *exogenous factors*.
2. That of the *endogenous factors*.

Among the *exogenous* factors is included the greater part of those numerous and diverse theories which have sprung up around this question, induced by the luxuriant fertility of the imagination rather than

attained through the slow and cautious development of a scientific process.

St. Lager cites 378 authors and 42 different opinions, some of which, such as the influence of weather, light, temperature, racial conditions, mechanical injuries, configuration of the soil, etc., are evidently untenable because of the wide distribution of goiter.

A causal influence has been attributed by Saussure to want of sunshine and to lack of renewal of the air in the deep-laid mountain valleys; by Gosse, and more recently by Chopinet, to the humidity of the soil; by Lizzoli to air containing too much oxygen; by Fodéré and Niepce to climatic conditions. Heidenreich attributes to the moon an influence upon the thyroid gland. Various conditions of the atmosphere have been incriminated, such as air charged with sulphurous vapors, or electricity, or air wanting in iodine, or air that is too cold or too dry, and so forth.

Social and economic conditions have been considered the cause of goiter by many French and Italian writers. But the evidence before us seems to establish definitely that all social classes and conditions suffer from goiter. Neither the rich nor the poor enjoy a special immunity, although there would seem to be some relation between occupation and the development of goiter since the mining and agricultural classes in endemic territory are more subject to the disease than others. This fact suggests that the close contact of these laborers with the soil might be an etiological factor.

Hanshalter and Jeandelize observed a considerable diminution in the intensity of the endemism in that ancient goiter center Rosieres, Department of Meurthe et Moselle, after the introduction of waterworks and improved sanitary conditions, and therefore concluded that besides microorganisms, hygienic conditions play a predominating role in the etiology of the disease (*loc. cit.*, Bircher).

Some authors have attributed an etiological influence to the habit of bearing burdens upon the head, but as this custom is confined to narrow territorial limitations, while goiter is as widespread as the inhabited earth, this theory is evidently false. The very wealth of publications and hypotheses on the subject renders the necessary selection and elimination an exceedingly difficult and perplexing process. The greatest criticism that can be made of most of the theories advanced is that they have been elaborated to fit certain circumscribed areas only. They are thus rendered valueless, as they do not grasp the problem as a whole, but discuss some phases of it only. Consequently it becomes necessary to read, weigh and compare all of these diverse views, seeking the connecting link where scientifically established facts are recorded, and setting aside such evidence as is purely circumstantial. In all the liter-



ature concerning goiter which has come down to us throughout the ages there is but one conclusion which is constantly and predominatingly present, *i. e.*, the *relation existing between water and endemic goiter*.

**The Relation between Water and Endemic Goiter.**—This relation has been popularly accepted from the earliest times, and among the ancients certain springs, wells and rivers were reputed as goitrigenous and their water avoided for drinking purposes. As, for example, in Chios where an inscription was placed above a well warning the thirsty passerby that this water rendered those who drank of it dull. Another such well existed in Beotia, near the River Orchomenes, and was believed to cause loss of memory; likewise the Red-well in Ethiopia and the Gallus River in Phrygia were supposed to affect the mind. Ovid said, “. . . sunt qui non corpora tantum verum etiam animos valiant mutare liquores.” Hippocrates, Aristotle, Galien, Celsus and Pliny discuss at length the mysterious virtue and power of these strumigenous springs and mention those of the Apennines, of Phrygia, of Chios and Creta. Vitruvius wrote of the people inhabiting the Maurienne Valley where the endemism prevails with intensity to this day: “Acquiculus in Italia et Alpihus, nationi Medullorum est genus aquæ, quam qui bibunt efficiuntur turgidis gutturibus.” Agricola, 1546, notes a well in Coire, “Cujus aquæ potæ adeo lædunt cerebrum ut stolidos faciant,” and as early as 1574 Josias Simler in the Canton of Valais, and Felix Platner in 1614 in Bale, endeavored to establish clearly the relationship already perceived by the ancients between certain waters and some kinds of tumor of the throat, often associated with a form of degeneration where idiocy and arrested physical development were combined. In 1680 J. Wagner, in Article 18 of his *Natural History*, enumerates the goiter-wells in the Cantons of Berne, Grisons, etc., among which he mentions Fons Regis of Berne. In more modern times the goitrigenous properties of certain wells were so generally accepted that young men liable to military service drank of these waters in order to acquire goiter and thus to escape military duty. These facts are reported concerning wells in Argentine, Pantamafrey, Villard-Clement, St. Chaffrey and Cavacurta in Lombardy, of which last Lombroso writes, “La fonte del gozzo ove sogliono andare i giovani all epoca della coscrizione onde acquistare in quindici giorni quel difetto che li sostræ dal servizio.” (The goiter-fountain which is visited by youths at the time of conscription in order to acquire this infirmity in two weeks, and thus avoid military service.) In reference to this well, it must be said, however, that Kutschera quotes Grassi and Munaron as having examined the well and as having established the fact that no one in Cavacurta knew of its possessing the injurious properties attributed to it, and further, that goiter has never been endemic in this locality. In connection with these findings of Grassi

and Munaron we might recall that St. Lager affirms that the authenticity of these statements was investigated by him personally and confirmed by the testimony of reliable persons such as priests, doctors and magistrates.

We can, I think, accept as an established fact that the goiter causative factor, whatever its nature may be, is most frequently conveyed to the human organism through drinking water. The general consensus of opinion among investigators concurs in this point, although differing in all other things. The most convincing proof in support of the infection of drinking water is furnished by the many reliably observed and recorded cases of individuals, newcomers from goiter-free territory to the endemic area, who rapidly acquired hyperplasia of the thyroid gland after drinking the water from these goitrogenous wells, and whose swelling as rapidly subsided after they ceased the use of the water. Many of these epidemics already mentioned seem to be collective experiments in this sense, and merely deserve the name epidemics because occurring in groups instead of in individual cases, from which they differ in no other respect.

Many instances are recorded where boiling the drinking water sufficed to prevent the occurrence of goiter in endemic territory, as in the case reported by Breitner, of a railroad linekeeper's family where father, mother and seven children all acquired enlargements of the thyroid gland upon drinking water from a goiter well. Breitner advised boiling the water before using it and within four weeks the swellings had visibly diminished. Later, this family again drank the unboiled well water and the swellings at once recurred. Numerous cases are recorded where the use of rain water was sufficient protection against the endemic disease. Dr. Mottard cites the case of a citizen of Bourieux, Maurienne, who constructed a cistern for rain water and thus preserved his family and neighbors immune in the midst of the endemism, by the exclusive use of this water.

Billiet and Boussingault report similar cases. Mgr. Billiet knew of but one family in Planaise exempt from goiter, and in this household rain water was used exclusively for drinking purposes. Baillarger reports a case observed by Dr. Housseaut in Grozon where the railroad employees acquired goiter within a short time after their arrival in endemic territory. In answer to their complaints the railroad company built a cistern and from this time on the employees remained free from goiter.

Further observations as to the immunity of rain water from the goiter agent have been made by Kocher, E. Bircher and others. Of special significance is the case observed by Dr. Gauthier in Fort de l'Ecluse and reported by H. Bircher. The garrison of the upper fort drew their drinking water from a cistern and were free from goiter,

whereas the lower fort used spring water and goiter became prevalent among the troops.

John W. McClelland reports an endemic in Deoba, India ("Some Inquiries in the Province of Kemaon Relative to Geology Including an Inquiry into the Causes of Goiter," 1835, printed in *Dublin Jour. of Med. Science*, 11, 295, 1837), which is of special importance for the drinking-water theory of the etiology of goiter. The Brahmins or highest caste of the population were entirely free from the prevailing endemic, their water supply being brought in pipes from a distant spring, and to this supply the other classes had but partial or no access. The middle caste (Rajputs) drank partly good and partly goitrogenous water, and were two-thirds goitrous, while the lowest class (Domes), who were dependent for their entire water provision upon the local goitrogenous springs, were goitrous throughout. Kutschera, however, considers this case as a proof of the infection by contact theory, and explains the upper caste's exemption from the endemism not because of the use of different water, but rather in the complete separation and isolation of the Brahmins from the infected lower castes.

The peculiar and interesting conditions of the endemism in the village of Antignano have already been mentioned, where of the three wells used by the inhabitants, one caused goiter, the second goiter and cretinism, while the third was free from both deleterious influences.

Avillard suffers only in winter from goiter while using well water, and the disease ceases during the summer when the inhabitants drink snow water.

When in Longematte (Savoy) the spring-water supply was cut off, and it became necessary to sink wells, goiter immediately ensued.

Humboldt reports from Colombia that until 1870 there was no goiter in Maraquita and the plateau of Bogota, while the disease was endemic in the rest of the Magdalena Valley; up to that time the population of this goiter-free region drank only river water, and it was not until well water came into use that goiter occurred. It has been observed that goiter may be produced or eliminated by a mere change in the location of wells, as in the case of Saillans and Saxon in Valais, and Nozeroy (Jura). On the other hand, in Nottingham goiter appeared when it became necessary to sink the already existing wells deeper.

Numerous authors have cited examples of rivers and streams, which, although goitrogenous at their source, lose this property during their course, and *vice versa*, streams which were innocuous originally may become infected during their course, probably through the addition of water from goitrogenous springs and streams. Those authors who believe in the telluric causation of goiter, attribute this acquired contamination of a stream to its passage through certain geological formations

such as marine deposits of the Palaeozoic age, or Triassic and Tertiary strata, etc.

Almost classical has become the history of the decline of goiter and cretinism in Rupperswil where, upon the advice of H. Bircher, a change in the water supply was made in 1886, when water from a spring in the goiter-free Jura was conveyed to Rupperswil, with results as given in the following figures by H. and E. Bircher:

1885 . . . . .	59.0 per cent. goitrous
1886 . . . . .	44.0 " "
1889 . . . . .	25.0 " "
1895 . . . . .	10.0 " "
1907 . . . . .	2.5 " "

E. Bircher considers his observations in the village of Asp even more important than those of the village of Rupperswil. In 1863 the statistics of this village showed 34 per cent goiter, 8 per cent cretins, 15 per cent deaf-mutes. The drinking water was of shelly limestone derivation. In 1907 the upper village introduced a new water supply, the lower village, however, continued to employ the old system. In 1910 the conditions resulting from this change were the following: Upper village, 6.4 per cent goiter, 8 per cent adults and 5 per cent school-children; lower village, 38 per cent goiter, 20 per cent adults, and 66 per cent school-children. In the lower village this endemic could be traced to the individual houses which were not connected with the new water supply. As a counterpart to these two examples, E. Bircher cites the community of Densbüren, which in 1908 brought a new spring-water supply from the shelly limestone formation to replace that from the Jura used before. Within three years after this change was made Bircher found a high percentage of goiter among the school-children. The exactitude of the results quoted above obtained by change of drinking water in the last three cases has been contradicted by Drs. Dieterle, Hirschfeld and Klinger in an article which appeared in the *Münchener medizinische Wochenschrift* for August 10, 1913, and to which I shall refer later in connection with Bircher's theory concerning the influence of geological formation upon endemic goiter.

That the activity of the goiter causative factor is of an evanescent and fleeting character has been proved by numerous observations. It is destroyed by ebullition, and though not destroyed by filtration, it is appreciably diminished. Water which is gathered into reservoirs loses its goitrogenous properties after a certain period of time, as does water transported and allowed to stand in bottles or casks. Boussignault cites the case of a family living in endemic territory whose members preserved themselves from goiter by the simple precaution of letting the



drinking water stand two days before using it. Often canalization or piping of streams suffices to destroy their harmful power. The village of St. Chaffrey furnishes us with a curious illustration of this condition; the water from a brook after being carried a few hundred meters in closed pipes to the village is entirely inoffensive, whereas at its source this same brook water is intensely goitrigenous. It is said that at the time of conscription the youths of St. Chaffrey have not omitted taking advantage of this convenient situation in proximity to a goiter fountain, and have frequently traversed this short distance in search of a goiter exemption (Berard).

At St. Jean du Maurienne the endemism disappeared within a few years after the introduction of a new water supply which was carried in subterranean pipes from a spring at Jarrier near St. Pancrace, although this new water supply was obtained from the midst of endemic territory (Repin).

St. Lager observed that in the village of Chateldon in Auvergne the canalization and collecting into a reservoir of torrent water was sufficient to render the water innocuous.

The value of decantation in arresting the activity of the goiter principle is demonstrated by an example cited by Thea in 1903 in *Il Policlinico*. In the town of Cuneo 40 per cent of the soldiers in the garrison became goitrous in the space of five years; treatment remained ineffective in Cuneo, but there was an immediate amelioration upon change of residence. The general population remained entirely unaffected, although using the same drinking water which was collected in vast reservoirs and drawn off for distribution from the upper part of the last basin. Upon adoption of the same disposition for the barracks the goiter epidemic ceased.

Goiter diminishes, disappears, or occurs in conformity with certain changes in the drinking water whether naturally or artificially produced. The case of Bozel in Tarentaise is a typical example of the effect upon goiter of such a change in the water supply. In 1848 the Sardinian Commission counted 900 goitrous individuals and 109 cretins in a population of 1472 souls, while the inhabitants of St. Bon at 800 meters' distance on the opposite slope of the valley were entirely free from such infirmities. Between the peasants living in these two villages there existed no essential differences in houses, food or habits. The degree of material prosperity was the same. The Community of Bozel, realizing that the only appreciable dissimilarity was in the drinking water, brought water to Bozel from a spring in St. Bon, and since that time goiter and cretinism have almost entirely disappeared. Berard reports in 1907 that in the neighborhood of Bozel and Brides he observed only a few small goiters.

The waters of the Alpine torrents have frequently been incriminated as causing goiter during the summer months when they are gray and filled with deposits from the glaciers and melting snows. The fact is that during this season the overland streams become unfit for alimentary purposes, because of the quantity of organic and inorganic matter washed into them by the heavy spring rains and the melting snow; consequently, in many places where water from non-goitrigenous streams is ordinarily used for drinking purposes the peasant is obliged to have recourse to wells, although frequently aware of the danger he incurs; thence arises the misconception as to the goitrigenous properties of these mountain torrents at certain periods of the year.

The *endogenous factors* include personal predisposition, heredity, sex and age. In goiter epidemics it has been constantly observed that when a group of people is exposed to similar goitrigenous influences the degree of resistance to the disease varies with the individual, some acquiring goiter within a few weeks, others only after many months, while a certain proportion is altogether refractory to the disease.

All of the inhabitants of endemic territory being equally exposed to the endemic noxa, it remains a matter of conjecture why some of the inhabitants of these countries remain refractory to the disease. Repin is of the opinion that under exactly similar goitrigenous influences individual temperaments will respond positively or negatively according to their preëxisting tendencies toward rapidity or retardation in the metabolic exchanges.

The fact that the ingestion of goitrigenous waters does not occasion goiter in an individual case does authorize the conclusion that this individual possesses a kind of immunity to the disease. What this immunity consists of has not yet been established.

*Heredity* is so much involved in predisposition and individual temperament that it is difficult to assign to either a separate and distinct place among the etiological factors of endemic goiter. There seems to be no doubt that the endemic noxa acting upon successive generations of families living in the goiter zone acquires an accumulative effect. For instance, many cases are known of families who have emigrated from immune into endemic territory where the first generation acquired goiter, the second showed symptoms of the cretinoid degeneration, and the third generation developed cretinism. It is a well-established fact that the children of goitrous parents are more liable to have goiter than the children of normal parents, and congenital goiter, which is not rare in endemic territory, may be said never to occur without goiter in the mother. Numerous cases have been observed and reported of mothers who have emigrated from endemic territory, and whose children, born and brought up far away from the influence of the endemic

noxa, have nevertheless developed goiter. In the case of one family that has come under my observation, the grandmother, a goiter-bearer, had emigrated from endemic territory in her early youth; she settled and married in immune territory, where her three daughters and four grandchildren were all born; they all developed goiters. In the family of one daughter with two goitrous children, the husband's children by a previous marriage, although living in the same household, were absolutely normal, so there could hardly be a question of infection by contact.

The same has been noted, although less frequently, where the father is a goiter-bearer. In one or the other of these categories may be placed most of the cases of sporadic goiter which are not due to endemic influences, but it must not be forgotten that the endemism may be so light that only such individuals as are highly predisposed will suffer from its effects, and this predisposition is itself a family tendency.

Due allowance being made for all other determining conditions, there is undoubtedly less resistance to the cause of goiter in certain families than others, just as the tubercle bacilli are able to establish themselves with greater facility in predisposed families than others.

Billiet, writing in 1835, remarks that after emigration from endemic territory the hereditary tendency slowly disappears, a complete cure being effected only in the third generation.

It is difficult to determine to what degree the hereditary tendency is an acquired characteristic. Schittenhelm and Weichardt have collected family histories showing the development of an acquired hereditary tendency in families having emigrated from immune to endemic territory. It is clearly established that the dreadful sequelæ of endemic goiter—deaf-mutism and cretinism—are due to the progressive and cumulative effect of the endemic noxa upon successive generations. Cretinism occurs only where endemic goiter prevails. Where the endemism is light only goiter is found, and in proportion to the severity of the endemism the number of cretins and deaf-mutes increases. Statistics show that 80 per cent of cretins are born of goitrous parents.

Goiter in the mother is of greater influence upon the children than in the father. It is, however, evident that goiter in the parents cannot be considered the cause of cretinism, as it is only in endemic territory that cretinous children are born. A goitrous mother will not bear a cretinous child unless subjected to the endemic noxa. Even cretinous mothers may bear *intelligent* children when removed from endemic territory. This fact was understood by the women of Sion, Sierre, etc., in the Canton of Valais in Switzerland, who having given birth to cretinous children at home, found that by passing the period of pregnancy and birth outside of endemic territory they were able to bear more healthy children. Especially interesting and curious are the cases which have

been observed from time to time of normal children born in cretinous families where among five or six children bearing the stigmata of cretinoid degeneration, one is born and remains healthy physically and mentally, although subjected to the same cretinogenous influences and the same daily contact as the other members of the family. This observation has led Cerletti and Perusini to conclude that the cretinogenous injury must be acquired during the intra-uterine life and is not transmitted at the time of conception. Before, however, drawing conclusions too easily, one ought to be sure that the paternity is the same in every instance.

**Hydrotelluric Theory.**—If we accept as an established fact that the goiter germ, whatever its nature, is most frequently conveyed to the human body through drinking water, the problem which at once presents itself to the investigator is to determine by what means the water acquires the harmful properties in question. This problem remains unsolved to this day despite the most intensive scientific researches. Chemical analysis has not discovered anything of importance nor does spectroscopic examination reveal unusual elements in goitrogenous waters. Many theories that have seemed true in one part of the world have not been substantiated when applied to a wider field of investigation. Grange attributed goiter to the presence of magnesium in the water. St. Lager, to the presence of iron and copper pyrites. It is undoubtedly true that goitrogenous waters are frequently heavily charged with lime, an observation which was made by McClelland and others and led to the belief that hard water, or waters containing lime in large quantities are goitrogenous, and that waters in which this ingredient is entirely absent do not contain the goiter causative agent. On the other hand, Christener asserts that the Weissenburg hot lime waters are beneficial in the treatment of goiter, and Zschokke reports that the use of Biberstein water, of which lime is a predominating constituent, causes goiter to disappear.

Since no sufficient cause for the endemism could be found in the metallic and chemical constituents of the water, it was thought that its harmful effects might be due to the absence of some necessary element such as carbon dioxide, salt, absorbed air, or more especially iodine. Unfortunately for the latter theory, analysis has proved that goitrogenous and even non-goitrogenous waters frequently contain the same quantity of iodine, and instances are known where water particularly rich in iodine causes goiter, as in the case cited by Chatin at Beaulieu in the Department of Oise. On the other hand, it must not be forgotten that excellent results in the treatment of goiter have been obtained by the exclusive use of distilled drinking water.

Many investigators are convinced of the parasitic origin of goiter.



According to our actual knowledge of the disease and its cause, it seems probable that in this direction must lie the ultimate solution of the problem, but until now, in spite of the highly perfected means of investigation possessed by modern science, it has been impossible to isolate the microbe. Countless experiments by many investigators have led to no positive results. Ewald says, "If water be of influence in the origin of goiter—and this does not admit of doubt—the cause can only lie in a *contagium vivum*, or organic poison." Schittenhelm and Weichardt find that the general mass of evidence indicates a parasitic infection of the water. This is also the opinion of McCarrison and many others.

From the earliest days of scientific research as to the etiology of endemic goiter to our own times, many investigators have sought to establish a correlation between certain geological formations and endemic goiter. The fact that the quality of the drinking water must be influenced by the character of the soil from which it springs has led to the association of these two elements.

Virchow, in summing up the results of his researches concerning cretinism in Lower Franconia, writes, "I hold the nature of the water to be the essential factor, but believe this to be determined by the geological formation of the soil from which it springs." Kocher considers drinking water as "the only paramount factor through which the soil could exercise such a determining influence upon the health of the inhabitants as in the causation of endemic goiter." Cardinal Billiet, whose investigations were made in Savoy, was among the first to follow this line of research, and as early as 1835 maintained that goiter was endemic on the argillaceous, calcareous and micaceous schists, and absent on the Jurassic and cretaceous formations. McClelland at about the same period made investigations in Kumaun, in the Himalayas, where his observations led him to conclude that the argillaceous schists, siliceous sandstones, amphibolites, granite and the micaceous slates were free from goiter, which prevailed with intensity on limestone formations. McClelland further writes, "The exciting cause has been traced to certain strata of the earth under circumstances calculated pointedly to suggest that water is the medium by which it is conveyed to the bodies of men."

Grange, who studied the question in the Alps, considers excess of magnesia in the water to be the cause of goiter. He finds that while goiter exists on the marine Molasse, it is most prevalent on the Triassic formations, *i. e.*, the shelly limestones, marl and especially the magnesian limestones of the Dolomitic formations. He found the coal and granite formations free. These conclusions of Grange have been corroborated in Germany by Virchow, who finds the shelly limestone (Muschelkalk) of Lower Franconia intensely infected, while a decided

retrogression of the disease upon the Keuper and sandstone of Middle Franconia is observed. The same findings are reported by Meyer, Diedel and Heidenreich in Middle Franconia. In France, Garrigou finds the disease associated with the marl and Dolomitic clays of the Pyrenees and New Granada. Boussignault reports the endemism prevalent on the limestone rocks. In 1843 Escherich found goiter prevalent in Lower Swabia on the Keuper and shelly limestone (Muschelkalk) and absent on the Jurassic formations of Upper Swabia and the chalk formations in England and France.

De Beaumont has demonstrated in Savoy that Jura granite and chalk are free from goiter, while on the Eocene and Triassic formations the endemism is intense. St. Lager, to whom we are indebted for important investigations as to the causes of goiter and cretinism, has made a most careful study of the geological conditions existing in goitrogenous regions and has concluded that while ordinarily, granite, gneiss, mica schists and the quartziferous porphyries are free from the endemism, this is not true when they are covered with a superficial stratum of metalliferous rocks. Although rare on volcanic soil, goiter is found near the solfatara, where the sulphurous emanations attack the ferruginous clays. The endemism is to be found on the magnesium limestones of the Lias, on the red clays, on the dolomite and gypsum of the Trias, and on the Molasse. On alluvium or diluvium the disease does not exist unless this soil has been transported from goitrogenous regions.

According to St. Lager, the endemism coincides with the existence of metalliferous and silicious rocks, the influence of iron pyrites being particularly injurious. Baillarger finds goiter widely disseminated on Dolomitic rocks in France. Hirsch, in his general summing up of the situation in 1860, concludes that although no geological formation precludes the possibility of occurrence of goiter or cretinism, both diseases are far more prevalent on the older formations, including the Trias group, than on the newer strata. Thus the general consensus of opinion among investigators seems to indicate a probable relation between the character of the soil and endemic goiter, the injurious influence upon the human organism being attributed to the mineralogical or geological structure of the soil.

The *hydrotelluric theory* of the etiology of goiter received its most important contribution in 1883 from H. Bircher in his valuable and interesting monograph on *Endemic Goiter*. Bircher observed that the endemism prevailed with intensity among the villages situated on the right bank of the River Aare, where the soil formation was marine Molasse, while among the inhabitants of the villages situated upon the Jura formation of the left bank goiter was absent with the single exception of one village, which stood upon a strip of Muschelkalk (shelly limestone)

extending into the midst of the Jurassic formation. Bircher based these observations upon personal examination of the school-children in this region, his home district. He next proceeded to consult the military statistics, with the result that his previous findings were verified, not only for the Canton of Aarau, but also for the whole of Switzerland. Upon further extended and painstaking researches he became convinced that in Switzerland, which is of all European countries the most severely afflicted with goiter, the disease only occurs upon the sediments of Triassic, Eocene and Miocene seas, and that the Jura and chalk as well as the fresh-water deposits are free from goiter. Furthermore, after studying the geological conditions in relation to endemic goiter in other countries, Bircher concludes as follows:

1. Goiter only occurs upon marine deposits and especially upon marine sediments of the Paleozoic, Triassic and Tertiary periods.

2. That the eruptive rocks, the crystalline rocks of the Archaean groups, the sediments of the Jurassic, Cretaceous and Quaternary seas and all fresh-water deposits are free from goiter.

When the disease is found on geological formations of the second class, this is due either to the fact that this formation consists of a comparatively thin layer covering a substratum of rocks of the first class, so that the sources of springs and wells are not derived from the superficial upper stratum, but extend into the underlying rockbed, or, to the fact that these goiter foci may be located on isolated islands of rock of the first class which, when covering any considerable area of the earth's surface, form the garden soil of endemic goiter. On the other hand, the injurious influence of such formations may be lessened or may entirely disappear by superimposed fresh-water deposits, the endemism occurring only where the underlying marine strata breaks through the fresh-water sediments. Bircher explains the greater frequency and intensity of the endemism in mountainous regions by the fact that in bursting through the earth's crust, the older strata of the Paleozoic and Mesozoic periods have been pushed to the surface, as is especially the case in the Alps. In other parts these strata have been so elevated that the later seas never covered them as with the Trias on both sides of the Rhine. This is also the explanation of the prevailing endemism in central Switzerland and Styria, where the Miocene marine deposits form the upper stratum of the earth's crust because of the continental elevation which prevented the superimposition of later sediments.

Low-lying river valleys are also frequently goiter centers because the stream cuts through the earth's crust and uncovers the underlying formations, bringing them to the surface, where they necessarily produce their pernicious effect upon the drinking water.

In support of these conclusions of H. Bircher, his son, E. Bircher,



has contributed a very valuable mass of evidence obtained from investigations and experiments which have been executed with the utmost care and attention to detail. One of these experiments is particularly interesting in having a special bearing upon the matter under consideration.

In an early publication Bircher recorded an unsuccessful attempt to create artificially goitrogenous water by placing sterile water in direct contact with rock of one of the formations upon which Bircher affirms that goiter occurs. The failure of the first experiment he attributed to defective preparations, probably due to the fact that the rock used was taken from the mouth of the Rupperswil spring, while the infection of the water was doubtlessly drawn from the substratum with the source of the spring itself.

For his later experiment he used stone from the middle marine Molasse. After placing a cubic meter of this rock in a wooden receptacle, he filled the receptacle to the brim with distilled water and allowed the water at first to remain in contact with the stone from ten to fourteen days, but later only three days. This water was given to rats to drink. After a period of about nine months, the rats subjected to this experiment developed hyperplasia of the thyroid gland.

Bircher considers that the results obtained from this experiment clearly connect the cause of goiter with the soil and furthermore proves that it is limited to certain geological formations. As to the actual primary cause of this infection, Bircher acknowledges that it is still unknown.

It is at present impossible to determine whether the cause, whatever its nature, is due to purely chemical processes within the rock itself, or whether the active generating principle of the goiter must be sought in a living organism which finds its culture media on the geological formations incriminated. Personally, Bircher is convinced that the goiter toxin is of colloidal nature and that it is washed or soaked out of the rocks by water. He also made a number of interesting experiments upon rats in order to prove that the goiter-causing substance must be in a colloidal state. In these experiments, he finds that these toxic substances are not removed from water by filtration through a Berkefeld filter, but that dialysis removes the goiter-producing substance from water, and that the substances separated from the water and remaining on the membrane of the dialyzer are likewise capable of producing goiter.

Animals experimented upon acquired goiter when drinking water from goiter springs both in the natural state and after having passed through the Berkefeld filter. No thyroid enlargement occurred when rats were given water that had passed through the dialyzer, but when the substances separated from the water by the membrane were fed to them they rapidly acquired goiter, the degenerative changes in the



cells of the thyroid gland being peculiarly severe. As the goiter toxin cannot go through the membrane of the dialyzer, it must, according to Bircher, be of colloidal nature. Moreover, through centrifugation water from goiter-producing springs may be rendered innocuous, and as it is an established fact that colloid substances may be coagulated when centrifugated, this is particularly significant. Many investigators have found that even severe shaking of the vessel containing goiter-producing water is sufficient to render it innocuous. Bircher finds that the general indications of these observations are decidedly against the probability that goiter is caused in a direct manner by a microörganism, as nothing in bacteriology has heretofore shown that water containing bacteria could be rendered harmless by standing, shaking or by centrifugation.

In more recent experiments Bircher found that goiter-producing water may become free from toxin by filtration through a layer of powdered charcoal 30 cm. thick. The success of this experiment, Bircher thinks, can only be explained by the colloidal nature of the toxin which admits of a process of absorption and is held fast in the powdered coal as the water passes through. The addition of various chemical substances to the water proved destructive to the goiter toxin. Zinc hydroxide  $\text{Zn}(\text{OH})_2$  is known to possess the property of separating colloidal substances in solution and the addition of 1 to 10 gm.  $\text{Zn}(\text{OH})_2$  to 1 liter of goiter water proved sufficient to render the water innocuous. The quantity of  $\text{Zn}(\text{OH})_2$  used was so small that it could scarcely have been bactericidal in its effect.  $\text{H}_2\text{O}_2$  even when used in exceedingly small quantities produced the same results. Finally, boiling renders goitrogenous waters harmless.

Bircher was able to demonstrate by the use of the stalagmometer that the superficial tension differs in goitrogenous and non-goitrogenous waters. The stalagmometer shows a considerable increase in the number of drops obtained from the goitrogenous water over the non-goitrogenous. Of the 57 waters examined, the 21 which were goiter-free showed about 56.45 drops, never exceeding 57.8, whereas the remaining 36 goiter waters showed an average of 60 drops, sometimes more, but never less than 59 drops. The capillary attraction would therefore seem to be lower in goitrogenous waters, and consequently its superficial tension would be lower.

Bircher next proceeded to make an ultramicroscopic examination of goiter water. At the time of his report he had examined eight springs in Aarau and vicinity. These goiter waters constantly showed a surprisingly large number of ultramicroscopic particles, or molecular constituents. These particles all presented the same appearance. They were round or slightly oval in shape, and showed the same continuous movements in all directions that are usually to be seen in substances

in a colloidal state, when under ultramicroscopic examination, as for instance, colloidal Argentinum nitric or colloidal  $\text{Zn}(\text{OH})_2$ . Whether these particles are of chemical or bacterial origin remains hypothetical.<sup>1</sup>

In summing up the conclusions of both H. and E. Bircher, Ewald remarks that while the indications are that goiter occurs only in districts of certain geological formations it is not always present where these formations exist. In fact there must exist a specific infection or pollution of these rocks for them to produce goitrogenous waters, and to such infection only the formations in question are liable, exactly as, for example, certain mushrooms can only grow upon soil of a certain character.

Johannesen corroborated these findings in Norway. His researches were carried out in a district where the geological conditions are simple and well known. He finds no goiter on the primitive rocks where these are free from an admixture of Mesozoic or Tertiary sediment. Of the goiter-bearers 96.6 per cent are to be found on the Silurian or Devonian formations. He cites one instance of a farm where goiter occurred, and which, according to the geological map, was situated upon primitive rock. Investigation, however, proved the map to be in error, and that the farm was lying upon the extreme limit of the Silurian argillate.

Höfler, in his researches concerning cretinism in the district of Tölz in Bavaria, reports the endemism intense in sections of the Miocene and Eocene formations, especially severe upon the Eocene flysch and upper shell limestone, and almost completely subsiding where the fresh-water Molasse and red sandstone predominate.

James Berry found that in England the endemism coincided with calcareous formations, prevailing not only on limestone, but also on calcareous sandstones (McCarrison).

Kocher did not altogether agree with the findings of Bircher. His own researches in the Canton of Berne led him to believe that goiter is not limited to the regions of the geological formations indicated by Bircher. With the assistance of 25 of his pupils he examined 76,606 school-children between the ages of seven and fifteen years, and found that in some parts of the Bernese Oberland from 80 to 90 per cent of the children suffered from the endemism. While the disease was far less frequent upon the Jurassic formations than upon the marine Molasse, he found that the former was, nevertheless, not exempt, and that even the upper and lower fresh-water Molasse were not immune. Kocher found the endemism intense upon the Jurassic formations of the Bernese Oberland. He was inclined to attribute these deviations in the behavior

<sup>1</sup> Das Kropf Problem von Dr. Eugen Bircher. Festschrift—Herr Dr. Heinrich Bircher.

of the endemism in sections situated upon similar rock formations, though in different parts of Switzerland, to the presence and admixture of impurities in the soil, and above all, to organic matter.

Kocher concluded that the determining factor does not lie in the mineralogical or chemical constitution of the soil, but in its greater or lesser pollution, and in consequence that the culture media for the microörganism or toxins involved may extend far beyond the limits indicated by Bircher (Ewald).

Investigations made by the late Dr. Ernest Pagenstecher in the middle Rhine district and in Nassau support in general the Bircher theory. He found the endemism most pronounced upon Devonian slate. Where this formation has been covered with a fresh-water formation the endemism disappears. Pagenstecher does not find the goiter especially pronounced among children in the sense of Schittenhelm and Weichardt.

In Hesse's researches concerning the distribution of endemic goiter in the Kingdom of Saxony, he was unable to corroborate entirely Bircher's theory as to the regular coincidence of certain geological formations and goiter. In Saxony, as elsewhere, the severity of the endemism increases within the high-lying mountainous districts, but in contradistinction to Bircher, Hesse found the greatest number of goiters upon the eruptive Muscovite gneiss and Ebenstock granite, while the Devonian, Silurian, and carboniferous formations of the Paleozoic periods were relatively free. In agreement with Bircher, Hesse found that the endemism was particularly intense upon the earliest strata of the marine sediment of the older Paleozoic period, especially the lower Cambrian.

Recent investigations were made by Lobenhoffer in Lower Franconia which entirely agree with the laws established by Bircher. Apparent deviations from these results were almost invariably found to be based upon errors in the geological map. These contraindications were corrected upon comparing the Lepsius map, which proved inexact in some places, with the more detailed Munich map. Lobenhoffer affirms that the intrusion of small wedges of shelly limestone amidst other formations will invariably augment the intensity of the goiter endemic. He believes these laws to be so exact that goiter may be considered a veritable Leit-fossil by the aid of which one can trace stratigraphical conditions despite errors of classification in existing geological maps. Where an apparent exception occurs, closer examination will prove either that a mistake has been made in classing the formation in question or that the outcropping stratum is of so little density that the springs and wells penetrate into an underlying bed of Tertiary, Triassic or Paleozoic marine sediment. These views are shared by Breitner, Wegelin, etc.



Schittenhelm and Weichardt recently made investigations in the Kingdom of Bavaria, where their findings did not, on the whole, agree with Bircher's theory. They report the endemism prevalent upon the Archæan rocks of the Bavarian Forest, and upon Keuper, fresh-water Molasse and Diluvium, all of which, according to Bircher's theory, should be immune.

Schittenhelm and Weichardt are convinced by their investigations in Bavaria that water issuing from one and the same rock formations may produce goiter in one locality and be harmless in another. Finally, they conclude that: "The primary determining factor for the endemic distribution of goiter does not lie in the geological formation but in the infection of the water itself, which may indeed be influenced by certain rock and soil conditions but not according to fixed laws." They further consider that the element most conducive to endemic goiter is the mountainous character of the country. It is interesting to compare this summary with the conditions which McCarrison groups together as ideal for the development of goiter: "An agricultural population living on a porous soil which soil contains much organic matter, and, because of its porosity or slope, admits of the ready passage of organic matter into the unprotected streams and wells that are the water supply of the people. It is in the mountainous countries where limestone rocks abound that these conditions are most frequently found in combination."

Schittenhelm and Weichardt further remark that the occurrence of endemic goiter in sections upon underlying Archæan rocks in but one region of the earth's surface would be sufficient to invalidate the Bircher-toxin theory, as it is impossible for an organic colloidal toxin to be washed out of Archæan rocks which are absolutely free from organic matter, or from eruptive rocks which reached the earth's surface with many thousand degrees of heat in a molten, liquid state. The most interesting observation made by these authors is related to the incidence of goiter among children which they claim reaches its maximum at about the tenth year and decreases after that age. The frequency of goiter among children is so great that it suggests an analogy with the findings of Koch in his investigations of malaria, a disease which attacked all children in endemic territory during early life, and was followed by the development of a natural immunity in the course of time. Schittenhelm and Weichardt suggest that in the regions where the goiter endemism is intense the entire population may be affected during early childhood in greater or lesser degree, the majority acquiring a sort of immunity later on. These observations are particularly significant when we remember Kocher's findings of from 80 to 90 per cent thyroid hyperplasia among the school-children of some parts of the Canton of Berne. It is, moreover, an established fact that the young are peculiarly liable to



develop goiter when transferred from goiter-free to endemic territory, as has been proved by the many epidemics in boarding schools, seminaries and barracks cited in the chapter on Epidemic Goiter.

While it may be considered as an established fact that the goiter toxin may be transmitted to the human body through drinking water (although even this is denied by some investigators, Kutschera, Tausig, etc.), few of the scientists of today still believe that the cause of goiter lies within the geological formation itself. We agree with Schittenhelm and Weichardt that "It is incredible that such virulent activity should be attached to a toxin derived from organic matter which has been buried within the earth for many hundred thousand years." More probably, when the solution is obtained, the cause will be found to lie within conditions which are quite subject to our control, as has been the case for so many devastating epidemic diseases such as malaria, yellow fever, and so forth. A curious fact is that in those countries where the endemism is light, although clearly defined, goiter wells are unknown, but as one advances into the districts of high endemicity, the noxious qualities of the waters concentrate and intensify until one comes to the well-known goiter fountains whose waters were dreaded even by the ancients and which have kept their evil fame unto this day.

It has been well said that the Panama Canal was built, not by engineers but by doctors, so why should their high courage, insight and perseverance fail before this oldest and most baffling of the endemism maladies? Through the process of elimination the circle of probabilities and possibilities must become smaller and concentration consequently higher in the remaining fields of investigation. The solution will doubtless come in this, as it has in other problems, when least expected.

**Repin's or Plutonian Theory.**—Dr. Repin, of the Pasteur Institute, has published several interesting articles upon the "Nature and Origin of Goitrigenous Waters," which he associates with mineral springs. As a general proposition he affirms that endemic goiter is never absent in a mountain range of any importance, and that in proportion to the height and precipitousness (*i. e.*, geologically recent) the endemism is more intense. The disease attains its maximum upon the mountain slopes and adjacent valleys and plains, the upper zone being comparatively free.

In order to make his theory clear, Repin gives a brief summary of the history of the origin of mountain chains. Mountain chains occur along lines of weakness in the earth's crust where there has been a subsidence or depression between two more rigid masses of the lithosphere. These lines of subsidence are called *geosynclinals*, and when through contraction of the earth's surface they are subjected to lateral or tangential

thrusts from the harder formations between which they lie, the space above them alone being free, these vast masses are folded, pushed upward, and forced one over the other in stratigraphical disorder. When this upheaval is terminated, those parts of the newly formed chain which are not on a firm basis subside and sink, the solid central mass usually maintaining its equilibrium while the slopes and base of the synclinal fold are rent with innumerable fractures and dislocations or faults.

The dimension of these fractures and the mechanism of their production indicate that the entire density of the lithosphere must be concerned. They therefore open a door of communication between the atmosphere and the igneous interior of the earth. The earliest of these fractures have been filled with incandescent matter which in the process of solidification has formed the veins of quartz, granite and porphyry, which we often find penetrating stratified deposits. Later these interstices formed chimneys where highly mineralized vapors condensed when reaching the cooler regions near the earth's surface and gave rise to the metaliferous veins so abundant in secondary and tertiary formations. At the present time only the most recent fractures remain open and the visible signs of the inner eruptive energy are limited to geysers, mineral springs and exhalations of combustible gas and carbon dioxide. Repin affirms that true mineral springs are precisely of this class and arise from great depths in the earth's interior through the aforesaid fractures of the lithosphere. They are known as *hypogene*, *native* or *plutonic* waters. Their most important attribute is the powerful action which they exercise upon the general metabolism, one which is possessed by no other medical agent. Analysis of the composition of these waters does not account for their peculiar and well-established property, which is transient and fleeting in character. These waters lose much of their action after transportation, and the best therapeutic results from their use are obtainable only at the source of the springs themselves.

Since the discovery of radio-activity it was natural for investigators to turn in that direction, and it was found that the majority of mineral springs were highly radio-active. Repin believes a high radio-active count to be a necessary condition of plutonic waters. In the great melting pot at the earth's center the water issuing from the liquefying rocks must absorb radium emanations in abundance and carry them to the earth's surface as it rushes upward through the lines of fracture already described.

Upon the foregoing basis Repin assumes the three necessary characteristics of mineral waters to be:

1. A general physiological action, *sui generis*, which he describes as affecting the general metabolism.

2. They must emerge along the lines of fractures in the earth's crust.

3. Their radio-active count must be high, this being (he considers) the necessary property of hypogene waters.

Repin believes these three attributes to be common to mineral and goitrogenous waters and that it is therefore legitimate to conclude that they belong to the same family, *i. e.*, that they are hypogene, native or eruptive waters. Examinations of goitrogenous waters from St. Jean-du-Maurienne and other goiter wells in the Maurienne, Oisans and Briconnais showed them to be radio-active in the same degree as the mineral springs of Dax and Contrexéville.

These native waters have been in contact with the igneous interior of the earth where aqueous vapors, mineral fumaroles, radio-active derivations and rare gases take part in a cycle of reactions from which results, under the appearance of a simple aqueous solution, a complex composition which we have not yet been able to analyze. This might be called the *plutonian theory*. Here, Repin recalls St. Lager's theory as to the etiological influence of metalliferous veins, especially iron pyrites, which he invariably found associated with goitrogenous springs; this erroneous conclusion being due to the fact that metalliferous veins and goitrogenous springs occur along the same lines of dislocation in the earth's crust.

To what element must be assigned the principal role in the complex aggregate which constitutes a true mineral water? Do the mineral constituents preserve a temporary instability which might facilitate their aptitude for entering into combination? For instance, the principal mineral substances found in goitrogenous waters are salts of lime and magnesium. In the Alps goitrogenous waters may frequently be distinguished from others by their calcareous deposits. But as these same mineral salts are also found in equal quantities in other waters which are manifestly not goitrogenous a causal influence cannot be attributed to them unless in these native or plutonic waters some unknown constituent might alter their action in the human organism. Possibly the energy developed by the disintegration of radio-active bodies has been employed in some abnormal biochemical process.

In short, Repin attributes capital importance to the chemical ingredients of goitrogenous waters, especially salts of lime or magnesium, in combination with radio-active substances. He bases this hypothesis upon the works of Senator, Leopold-Levi, de Rothschild, Hertoghe and others who have proved that the function of the thyroid is not single but is multiple. One function controls the metabolism of iodine, upon which depends the general metabolism; another function controls the secretion of phosphorus, which in turn presides over the thermogenesis, the vaso-

motricity, and the regulation of the cardiac rhythm; another function controls the secretion of sulphur, upon which depends the nutrition of the skin and hair; another function controls the secretion of arsenic, to an insufficiency of which Hertoghe attributes attacks of migraine. Each one of these functions is exercised by means of a special hormone which is secreted by a distinct mechanism, so that in fact the thyroid gland is composed, as it were, of a bunch of separate glands intimately associated and interwoven.

It will be easily conceived that when any of these functions is over-excited, one or more of the others is liable to become disordered.

In this connection Repin considers that the discoveries of Sabatani, J. Loeb and his school as to the biological action of the ion calcium are particularly valuable. These physiologists have shown that the ion calcium is a moderater of the cellular functions. Augmentation of the protoplasmic concentration of the ion calcium is accompanied by depression, while diminution of the concentration occasions phenomena of excitement. The thyroid gland is the regulator of the metabolic mechanism of the ion calcium and its opposing ion sodium. The influence of decalcifying agents, and especially sodium, is exactly opposed to that of salts of lime. Now, the work of Senator, Moraczewski, Papinian, Leopold-Levi, de Rothschild and others has established that the thyroid gland controls the metabolism of lime, and Repin holds it possible that in exercising its functional control over the general metabolism the thyroid gland may modify the concentration of the ion calcium and the ion sodium.

This much granted, Repin suggests a hypothesis which would cover all sides of the problem. Suppose that the ions calcium of goitrogenous waters differ from those contained in ordinary solutions by some one property—perhaps of an electrical character—and because of this difference are not subject in the same degree to the osmotic law, and are more readily diffused in the cytoplasm, where they remain in a higher state of concentration. In this case the ingestion of goitrogenous waters would induce a condition of hypercalcification from which would ensue a depression in the general metabolism. The effect would be that of a mineral water chemically characterized by a dominant lime and physiologically by a depression of the metabolism. These waters might be classified as the antagonists of those having a dominance of sodium. In this connection it is interesting to recall the statement of Leopold-Levi and de Rothschild that patients who have taken the cure at Aix sometimes show symptoms of Basedowism. Because of the hyperconcentration of the ion calcium, the thyroid gland is obliged to augment its secretion in order to maintain the chemical balance of the organism; hence hyperplasia of the gland; and if the use of water containing the



injurious ingredient is continued, the gland, being unable to increase its secretion in sufficient quantity to compensate for the hypercalcification, symptoms of hypothyroidism are added to the already existing enlargement.

E. Bircher remarks that these conclusions as to the biophysiological action of the goitrogenous waters in the organism must be considered as hypothetical in view of the fact that the metabolism of lime is controlled by the parathyroids and not by the thyroid gland itself.

Repin suggests that these facts might serve as a basis for a new treatment of hyperthyroidism. The tendency of goitrogenous waters being certainly to reduce the secretion of thyriodine, he believes they might be successfully employed in combating the hypersecretion of exophthalmic goiter. In support of this theory he cites a case reported by Prof. Wilms, of Basel, of a patient suffering from exophthalmic goiter whose condition invariably improved while living in endemic territory.

**Radio-active Waters and Goiter.**—Although radium has been used therapeutically in the human organism and experimentally on animals, and although it has been recognized that according to dose and methods of application, disturbances to health may ensue therefrom, and although mice, guinea-pigs and frogs have been killed by breathing air containing radium emanations in large quantities (several million mache units to the liter), it has, notwithstanding this, never been found that an enlargement of the thyroid could be attributed to the use of radium in any form. Further evidence in this direction is furnished by the large industrial class employed in handling highly radio-active substances. Prof. Dr. Hahn, of the Chemical Institute of the University of Berlin, after working with radium for six years, declared that although constantly occupied in an atmosphere containing radium emanations, exceeding the therapeutic dose a million times, he has never observed or heard of a goiter thus produced.

In Saxony there are certain districts where the endemism prevails with greater intensity than elsewhere, and this is particularly the case in Eastern Vogtland and Western Erzgebirge. Hesse finds that, orographically considered, the well-defined endemism may be said to prevail only in the high mountainous parts of the kingdom while the plains are relatively free.

The exceedingly varied surface of the land is naturally accompanied by an unusual wealth of geological formations due to great volcanic activity in the earlier phases of the world's history. It is therefore not astonishing that valuable minerals and metals should be found there in abundance. Large quantities of uranium minerals are also present, and because of the amount of radium contained in these minerals, the interest of those technically concerned with these products

has been aroused so that investigations have been made concerning them. Springs and waters were tested as to their radio-activity by order of the Kgl. Sach's. Finanzministerium, and thus it was found that Saxony possessed radio-active springs, and that some of these waters contain the highest amount of radium that has as yet been measured.

The results of these examinations placed at Hesse's disposition a considerable mass of reliable material for the comparative study of local correlations between radio-active waters and goiter. His conclusions are that the endemic goiter prevails most frequently in high-lying mountainous countries, and that here, because of certain geological and mineralogical conditions, strong radio-active waters are found in great numbers, but that such waters are as frequently found and are of equal strength where goiter is unknown. It may be concluded that there is no causal connection between radio-activity and goiter, and that the parallel coincidence of radio-active water and endemic goiter is accidental and not regular.

**Organic Theory.**—Prof. Wilms is of the opinion that goiter is due to an *organic ferment*. These views are based upon Bircher's experiments with goitrogenous water upon rats. Wilms thinks it impossible that a living organism should be confined to certain geological formations, and comes to the following conclusions:

During the formative process of the marine sedimentary strata, sea fauna must necessarily have been included in these deposits, which are therefore highly impregnated with organic substances. It is not improbable that water running through these sedimentary strata would wash out and carry off in solution some of the products of decomposition from these organic substances. The presence of these products in the water as toxin or organic ferments might then act as the exciting cause of endemic goiter. Wilms thinks that strong evidence in favor of this theory is furnished by Bircher's experiments proving that goiter can be produced in rats by water which has passed through the Berkefeld filter, and by Wilms's own investigations which have established that goitrogenous water when heated to 70° loses its harmful properties, this being the temperature at which toxins and ferments, especially toxalbumins, are rendered innocuous. From these facts Wilms concludes that the cause of goiter must be due to a *toxin* rather than to an *organic excitant*, and that this toxin is held in solution in the drinking water. Bircher believes the toxin to be of colloidal nature.

Dr. Sasaki, acting upon Prof. Wilm's suggestion, made a series of experiments with the view of studying the action of organic poisons in the production of goiter. These experiments carried out by Dr. Sasaki at Heidelberg gave the following results:

1. By feeding animals on cooked rice mixed with rat feces, moderate

sized enlargement of the thyroid gland of a diffuse character was produced.

2. Feeding with decayed fish gave negative results. The animals died rapidly and showed disturbances in growth.

3. By feeding with decayed meat, negative results were produced.

4. Feeding with calves' thymuses also gave negative results.

5. Subcutaneous injections with cadaverous products in large and small doses gave negative results. The animals died soon.

6. Subcutaneous injections of tyrosin also gave negative results.

7. Subcutaneous injections of acetonitrile gave negative results.

8. Feeding with rat feces mixed with iodide of potassium also gave negative results.

9. Feeding with rat feces mixed with thyroidin produced negative results.

These findings are exceedingly interesting and valuable, as they show that organic poisons are not capable of producing goiter, but that fecal matter contains a substance which may cause alterations in the thyroid gland when introduced into the circulation. Moreover, the addition of small quantities of potassium iodide or thyroidin to food which has been mixed with fecal matter was sufficient to prevent goitrous changes from taking place in the thyroid gland. All of these observations corroborate McCarrison's findings and coincide with the observations upon the retrogression of goiter among fish, after the addition of small quantities of antiseptics, sublimate or potassium iodide (solution 1-5,000,000) to the water of the fish tanks.

Interesting in this connection are the experiments of Dr. Fr. Messerli, of Lausanne (*Revue Médicale de la Suisse Romande*, March 20, 1915), in the treatment of goiter by intestinal disinfection. The disinfectants used by him were thymol, benzonaphthol, salol, creosote pills and mild laxative pills, the effect of which was merely to reduce the bacterial flora of the intestines by evacuation. In the 11 cases subjected to these different therapeutic measures the results were surprisingly good and have convinced Dr. Messerli that endemic goiter is coincident with the use of drinking water which in some way has been exposed to parasitic pollution. He does not know whether to attribute the results obtained from the antiseptic treatment to a direct action upon the specific goiter agent in the intestines or to a general effect in diminishing the number of normal microbes in the intestines and thus decreasing their toxic products.

These various experiments establish clearly that the goiter agent, whether living organism or toxin, is inhibited in its activity by the use of disinfectants.

Probably this restraining influence consists in a coöperative action

with the thyroid gland by means of which it is enabled to accomplish its normal task of counteracting and overcoming the ferments always present in the intestine, and at the same time to combat the specific goiter toxin. Such little assistance is sufficient to enable the gland to do all of this task without overwork, which results in hypertrophy, or in failure to accomplish the whole task, from which ensues the injurious and progressive accumulation of toxins resulting in goiter-heart and other phenomena of goitrous degeneration.

It must, however, always be borne in mind that no medical treatment is efficacious in cases of goiter of long standing, where severe degenerative, cystic and adenomatous changes have occurred. In all such cases there is no other recourse than to surgical treatment, which should be obtained at the earliest possible date.

**Contagion by Contact Theory.**—On account of long years of personal experience and investigations in Styria and Tyrol, Dr. Adolph Kutschera holds that the theory of the water etiology of goiter and cretinism is untenable. He is convinced that the only reasonable explanation of the various characteristics of the endemic lies in contagion by contact, and that there is no analogy in medical experience for the generally accepted opinion that the cause of goiter is to be sought *only* in the drinking water. In all of those diseases, he continues, the dissemination of which was for a long time attributed to water, it has ultimately developed that water was not the principal carrier of the infection. For instance, in typhoid fever, dysentery and cholera, water was supposed to be the exclusive source of the evil until it was clearly established that the principal means of transmission was through contagion by contact. Dr. Kutschera therefore assumes that such will be the case for goiter and for cretinism just as it has been for the foregoing diseases.

Before entering into the reasons which have brought him to this conclusion, the author defines his conception of cretinism in order to make clear the basis upon which he founds his theory as to the common etiology of these disturbances. This conception is based upon etiological reasons and not upon clinical observations, and includes all of the developmental disturbances, both physical and mental, which are caused by the cretinogenous noxa in endemic territory. Varying as this picture does from normal to the severest forms of hypothyroidism, idiocy and deaf-mutism, all of these disturbances can be traced to the same original cause. Goiter must, he declares, be included in these disturbances, but it bears a peculiar relationship to them; its general distribution is far wider than that of cretinism and outside of regions where endemic goiter prevails there is no cretinism. Cretinoid children, he continues, almost invariably have goitrous mothers, and in the rare cases where this is not true, either the father or another member of the family will be found to have goiter.



The most constant injury, adds Kutschera, that can be traced through all of the various disturbances occasioned by the endemic noxa is not goiter but injury to the nervous system. The endemic noxa acts upon the nervous system especially, and the severity of the disturbances occasioned are determined by the power of resistance in the individual attacked. The younger the child exposed to these influences the more liable will it be to acquire severer forms of the disease, as idiocy and deaf-mutism, while in adults and older children the result will be endemic goiter and its accompanying symptoms. Kutschera recalls that the thyroid gland is peculiarly susceptible to nervous influences, as has been shown in exophthalmic goiter; and he concludes that the goitrous agent works through the nervous system upon the thyroid gland, occasioning the cretinous degeneration when attacking the fetus or newborn child, and causing goiter in the adult, or more resistant body. Kutschera continues his arguments by showing that the general opinion that goiter and cretinism are confined to certain districts has been shown to be erroneous, and that this assumption was largely due to the exquisitely chronic nature of the disease which lasted a whole lifetime, its fluctuations covering decades and centuries instead of weeks or months, as in ordinary diseases. Cavatorti (1907) further illustrates that in Italy goiter has entirely disappeared from the Provinces of Ferrara, Bari and certain districts of Sicily, and that many other investigators report the endemics of both goiter and cretinism as diminishing or gone from localities where they formerly prevailed. Even more significant than these local and periodical fluctuations of the endemic he finds the fact that goiter and cretinism are not evenly distributed among the inhabitants in endemic territory, as would be the case were water the only cause of the disease. Dr. Kutschera concludes that careful examinations of all individuals living in groups of houses having a common water service show clearly that goiter and cretinism are not dependent upon the community of water but are confined to certain houses, and in large tenement houses may be traced to certain dwellings, *i. e.*, it is a house disease like tuberculosis.

Although cretinism is a pronounced family disease it cannot be considered hereditary, inasmuch as the parents of cretins are in general normal except that the mother in almost all cases has a goiter. Children of cretinous mothers may, and often do, develop normally if removed to a neighboring house where there is no goiter or cretinism. Köstl observed in 1855 that among the noblemen of the Canton of Valais it was customary to bring up only the eldest son at home while the others were left to the care of cretinous servants and likewise became cretins themselves. The necessity of dividing the property among so many children was thus avoided.

Kutschera bases his theory that goiter and cretinism in endemic territory are confined to certain dwellings, upon investigations made in nearly two hundred localities where he always found homes inhabited by cretins grouped together in close vicinity.

He did not find it possible to establish a correlation between the common water supply and the disease, as one and the same water was used in the cretin houses and in those free from the disease. Where one cretin was found, there were usually others in the house, and it was frequently shown that the house had formerly been occupied by cretins. Kutschera emphasizes this point in the hope that these conditions may be investigated in other localities. In 1844, Fradeneck described the Tostenhuben in the community of Sirnitz, Carinthia, where from time immemorial all children and adults suffered from the cretinous degeneration. These Tostenhuben which still exist were recently visited by Kutschera, who was unable to find either goiter or cretinism at the present time. Two of these Tostenhuben had been destroyed by fire and rebuilt. One had remained unoccupied during forty years and was then refurnished. Goiter and cretinism have since disappeared. In one of these "huben," which burned down in 1847, it was ascertained that a child born before the fire was still cretinous, while all the children born since the fire, among whom is the present proprietor, have developed normally. The water supply in every instance has remained unchanged.

Since the water cannot have been the cause of goiter and cretinism it must be assumed, Kutschera thinks, that the disease was transmitted by means of the household furnishing, bedding, clothing, etc.

The occurrence of goiter and cretinism outside of endemic territory furnishes further evidence in favor of contagion by contact. Kutschera recently encountered an unusually typical twenty-year-old cretin in a part of Tyrol (the district of Brixen) where goiter is rare and cretinism unknown. Investigations showed that all the members of the household, including mother, sister, and two little children boarding with the family, were goitrous. Further instances are given where in immune territory entire families may be found with goiter, the mother being a goiter-bearer from a region where the endemism prevails. Kutschera considers the already cited endemism in Deoba, India, where the Brahmin class remained immune as due to their complete isolation, and the consequent protection from infection by contact rather than to the difference in water supply to which it is attributed by McClelland.

Kutschera asserts that so-called goiter wells will not bear investigation. The stories of military conscripts having acquired goiter by drinking from wells in endemic territory is to be explained by their living with goitrous families where the disease was transmitted by con-

tact. According to his views all goiter epidemics are to be considered as evidence against the water etiology of goiter, as they never attack those having a common water supply, but are always confined to some one house or dwelling, such as barracks, boarding schools, etc.

The endemisms in fish ponds, cited by Gaylord, are also given as examples of infection by contact. Positive animal experiments in endemic territory are explained by the animals being exposed to contagion by contact. In closing Kutschera refers to Chagas's disease in Brazil, which in its chronic forms resembles cretinism and is transmitted from man to man by the bite of an insect. Kutschera thinks the discovery of this disease to be of the greatest importance for the etiology of endemic goiter and cretinism. Analogy is of such moment in medical matters that the possibility of the transmission of these endemic diseases through some intermediary host must be at least considered.

The fact that the development of goiter and cretinism is favored by unhygienic living might indicate the intervention of some species of insect.

Dr. Siegmund Taussig's researches concerning goiter and cretinism in Bosnia have led him to form the same conclusions as Dr. Adolph Kutschera concerning the infectious origin of goiter. Cretinism he believes to be a congenital condition due to goiter in the mother. In Bosnia and Herzegovina the opportunities to observe the dissemination of infectious diseases by contact are numerous because of the customs and habits prevailing among the population.

Through his observations in Bosnia, Kobler<sup>1</sup> became convinced that leprosy is transmitted by contact; moreover, it is noteworthy that in Bosnia leprosy is seldom found in large cities; that it attacks by preference the masculine sex (83 per cent) and that 44 per cent of those attacked are Mohammedans. (The latter constitute 32 per cent of the population.) The dissemination of syphilis in Bosnia has likewise attained most unusual proportions.

A recent governmental investigation showed not less than 42,000 cases of syphilis, the great majority of which were extragenital. A high percentage of the Mohammedan population was affected in this case also. These observations and his own experience as to the repeated occurrence of goiter in families brought the author to the conclusion that Kutschera's theory offered a possible solution of the goiter problem. From this point of view Dr. Taussig carried out extensive researches in Bosnia, especial emphasis being laid on family histories as a point most important for the contact theory.

The customs of these people are peculiarly favorable for the transmission of disease by contact. The population is almost entirely of the

<sup>1</sup> Ueber das Vorkommen und Bekämpfung der Lepre in Bosnien und Herzegovina, 1910.

agricultural class whose custom is to prepare and serve their food in a common vessel, from which each takes his portion without the formality or the intervention of forks, spoon or plates. Cups and glasses are likewise rare. The drinking water is kept in an earthenware jar from which all members of the household drink. Beds are almost unknown; everyone sleeps on the floor—members of the family side by side in the same room. These primitive customs are more prevalent in isolated and inaccessible localities, and are always accentuated in the Mohammedan families who cling to their old traditions with obstinate conservatism and accept modern customs with difficulty, whereas modern hygienic conceptions have been more rapidly absorbed by the Christian population.

Dr. Taussig's own observations rest upon these facts. In the garrison of 130 men at Srebrenica there has never been a case of goiter. It is true that the garrison has a water supply of its own, but this is obtained from the Bojnagebirge, whence the civilian population also draws its water supply. Among the families of officials and officers who have lived in Srebrenica for years and were scattered throughout the city, there was no goiter, with the single exception of one child who attended the public schools. Although the Austrian police are dispersed throughout the district, goiter is unknown among them. Dr. Taussig concludes that for the development of goiter there must be opportunity for repeated and close contact or association, and this being precluded by the religious and social differences between the native and foreign population, the endemism is not transmitted.

In the community of Gladovic, where the endemism is intense, there is an isolated group of houses entirely free from goiter and cretinism, although drawing its water supply from the same source as the rest of the community. Sarajevo, the largest city of Bosnia, is in general free from goiter and cretinism, although isolated goiters are to be found among the older inhabitants. Neither in the garrison of 4000 men nor in the families of officers and officials is goiter of frequent occurrence.

In the course of his investigations Dr. Taussig was informed that where goiter was contracted among the families of foreigners settled in Sarajevo, some one member of the family has first acquired the disease, the others becoming infected one after the other.

Dr. Taussig reports an interesting case which he considers has the value of an experiment in support of Kutschera's theory. On June 30, 1911, a fox terrier bitch owned by an army officer gave birth to three pups, of which two were males. Nothing unusual was noticed in the pups until August 7, when all three developed a swelling in the throat, which was pronounced goiter by the veterinary consulted.

When told of this occurrence the author immediately asserted that



these dogs had been infected by someone living in the house. Examination of every member of the household showed that the members of the officer's family were free from goiter. But the cook, who had been living in the family for two years, had a slight swelling of the thyroid gland, and the orderly, who was entering upon his third year of service, had a well-developed goiter which he had heretofore concealed by his clothing. This orderly had charge of the dogs which Dr. Taussig believes had been infected by him, as had the cook who came from immune territory and was unaware of her thyroid enlargement.

Epidemics observed in Bosnia and elsewhere, he finds, are always confined to members of the same household, the rest of the community, although drinking the same water, remaining unaffected.

Animal experiments are not conclusive because ordinarily carried out in endemic territory, and contradictory, opposite results are frequently obtained by different investigators. The fact that, in Gaylord's interesting observations of goiter among fish, the addition of an infinitesimal quantity of potassium iodide or sublimate to the water was sufficient to occasion retrogression of the goiter, indicates a parasitic origin of the disease. Dr. Taussig reports that in his examinations of cretinous individuals he made special inquiries as to the domestic animals and was never able to discover a single case of goiter or cretinism among them. Acting upon the assumption that the goiter virus is in the saliva, Dr. Taussig experimented upon a young guinea-pig and a young dog by mixing the saliva of cretins with their food. Both animals died within a few weeks, but the postmortem examination showed no enlargement of the thyroid gland.

Dr. Taussig sees a parallel case in the wide distribution of syphilis throughout Bosnia, where the general investigations made by the Government established the fact that the transmission of the disease was due to the use of common eating and drinking utensils, the primary and secondary lesions occurring in the mouth. Dr. Taussig concludes that endemic goiter is transmitted in the same way. The fact that the disease is more common in the Moslem than in the Christian population is further evidence in this direction because of the obstinate adherence of the former to their primitive customs and unhygienic habits of living.

Dr. Taussig finds a marked association between goiter immunity and the use of sea-salt. Countries which are either free from the endemic disease, or where goiter is rare, use sea-salt. This immunizing property is to be attributed to the iodine in the sea-salt, the constant ingestion of which in such minute and easily absorbed quantities is sufficient to increase the iodine supply of the thyroid gland and thus to destroy the goiter virus. Dr. Taussig believes that sea-salt is destined to play an important part in the prevention and cure of goiter, as it possesses the

immense advantage over all other therapeutic measures of being easily available for all classes, and, furthermore, that its use may be prolonged indefinitely without any ill result or disturbance of any kind.

Dr. Taussig is unable to accept Kutschera's theory that cretinism is acquired simply by contact. His researches in Bosnia and Tyrol have convinced him that cretinism is always congenital, but as the condition is difficult of diagnosis in a young infant, it ordinarily escapes notice until the child is a year or more old. The best proof that the cretinogenous injury must have taken place *in utero* is to be found in the several cases of cretin twins examined by Taussig in Bosnia and Herzegovina and by Cerletti and Perusini in Italy; in each case the clinical picture was the same in nature and degree for both twins.

Taussig's conclusions are that without goiter in the mother there is no cretinism. The mother who has been infected by the goiter virus has been injured in her reproductive power and consequently is frequently subject to miscarriage, premature birth, or the child is not viable. The children that survive are cretins. In time these manifestations become less severe, and the last children are usually in better physical condition. Nature seems to exercise an autoprotective process, the goiter virus and its injurious effects being ultimately counteracted in the system.

Dr. Taussig acknowledges that these very unusual phenomena are remarkably like what we know of syphilis, but he affirms that these observations were made not only in Bosnia, where syphilis is so widely distributed, but also in Styria and Tyrol, and that in the family histories taken by himself and the statistics consulted there was no syphilis.

There is no analogy between these findings of Taussig's and the conditions existing in regions of high endemicity in Switzerland, where miscarriage and premature delivery are not unusually frequent, although the rate of infant mortality is higher than elsewhere. Taussig found the results obtained in the treatment of cretinism by thyroid opotherapy unsatisfactory. Some degree of physical improvement ensued, such as increased growth and lessening of the myxedematous symptoms, but the mental condition remained unchanged. Any apparent improvement in this direction might be explained by the reduction in the myxedematous swelling of the mouth and pharyngeal cavity, so that the child is enabled to hear and speak with greater ease. He found, furthermore, that treatment with thyroid tablets, although continued through several years, resulted in no intellectual improvement.

**Infection Theory.**—Dr. Robert McCarrison, of the Indian Medical Service, in his *Etiology of Endemic Goiter* bases his conclusions upon observations and experiments made during ten years' residence in a part of India where endemic goiter prevails with great intensity. He

has further verified these conclusions by studying the disease in the various goiter centers of Europe and is convinced that the endemic goiter of Europe and Himalayan India are one and the same disease. He believes water to be the ordinary means of conveying the toxic agent of endemic goiter and bases his belief upon the positive results of his experiments in giving young men the residue separated by filtration from the goitrogenous water of Kashrote, and upon the animal experiments of Bircher, Marine, Lenhart and others. The toxic nature of the waters McCarrison attributes to the presence in suspension of a living agent which is the direct or indirect cause of the disease.

The characteristics of goiter produced experimentally in man are:

1. It appears about the fifteenth day of the experiment.
2. It shows a marked tendency to fluctuate in size.
3. It reaches its maximum in size between the twenty-fifth and thirtieth day of the experiment.
4. The enlargement of the gland is neither great nor progressive.
5. It is accompanied, as a rule, by certain subjective symptoms as, for example, throbbing in the neck, feeling of fulness and discomfort.
6. It may completely disappear under conditions of the experiment.

While McCarrison is convinced that water is the principal means of transmitting the contagium vivum of goiter, he also believes that the soil may become a vehicle. Any soil, no matter what its geological formation, may be converted into a suitable culture medium for the living cause of goiter through the presence of animal or vegetable matter. It is not the pollution of the soil or water in itself that is the cause of goiter. Just as polluted water will not cause typhoid fever unless it contains the *Bacillus typhosus*, so a polluted water will not cause goiter unless it contains the living organism to which the disease is due.

McCarrison believes that the seat of the infection in the human body is the intestinal tract, and considers that he has demonstrated the truth of this view by the results obtained in the treatment of endemic goiter by intestinal antiseptics. In more than 100 cases in which 10 grs. of thymol were administered night and morning the greater number were either entirely cured or greatly benefited.

This treatment is interesting especially because of its etiological significance. The germicidal power of thymol is very great and McCarrison believes that its action is either to destroy the living excitant of the goiter in the intestine or so to reduce its number and activity that the production of toxic substances is lessened and the thyroid gland thus relieved of the excessive demand for its counteracting anti-toxic secretions.

McCarrison also thinks that the well-known beneficial action of iodine is largely due to its germicidal properties. Further evidence as to the intestinal location of the goiter infection is afforded by the marked improvement of patients treated with lactic acid ferments (*Bacillus bulgaricus*). Remarkably brilliant results were also obtained by the use of vaccines. Having observed that a plentiful amœbic infection was present in the intestinal tract of sufferers from goiter in Gilgit, McCarrison endeavored to cultivate these organisms and was struck by the constant character of the bacillary growth which appeared in the medium employed. He prepared a vaccine from these bacteria and used it experimentally in the treatment of recent cases of goiter. No attempt was made to isolate any particular organism. The vaccine employed was therefore a composite one. A complete cure was effected in both cases where the vaccine was used. It was then noted that the bacterial growth referred to consisted largely of a bacillus which presented the main characteristics of the coli group. A vaccine was prepared from this bacillus, resulting as before in a complete cure of the patient treated. Vaccines were then made from bacteria not derived from the patient's own intestine. A staphylococcus vaccine prepared from a spore-bearing organism isolated from the feces of a goitrous pony were used successfully. The results from the use of Forster's dysentery vaccine were negative.

Metchnikoff has discovered that certain microbes of our normal intestinal flora are harmful by reason of the poisonous substances—indol and phenol—to which they give rise in the intestines. Organisms of the coli group, the staphylococcus, and certain spore-bearing organisms are among these normal inhabitants of the intestines which are responsible for the production of poisons, and the injurious action upon the liver, kidneys and arteries, as he has experimentally demonstrated.

Now the vaccines employed by McCarrison were made from organisms similar to these, and as there is no evidence at present that any of these organisms possess a specific influence in the production of goiter, McCarrison explains their action as follows: The function of the thyroid gland is to combat the poisons normally present in the human intestine, and if to these is added the specific virus of goiter, the gland unaided cannot suffice to counteract all these toxins, and thus, in the effort to perform its normal function and at the same time to destroy the specific goiter virus, the gland frequently undergoes hypertrophy, but if assisted in any one direction, it is capable of accomplishing the additional task without injury.

McCarrison summarized his evidence as to the intestinal location of the disease as follows: The toxic agent is introduced into the system through the medium of water or food, and since it is a well-known fact



that the thyroid secretion possesses to a high degree bactericidal and antiseptic powers, therefore a powerful antiseptic which exerts its action in the gut cures the disease just as the lactic acid bacillus, and the vaccines, which are prepared from organisms which are known to be normal inhabitants of the bowel, cause the disappearance of goiter.

In the microscopic examination of feces of goiter sufferers McCarrison very constantly encountered amœbæ, and while he says that no definite statement as to the pathogeny of these amœbæ can be made, their possible importance is obvious. Since 1906 he has been endeavoring to transmit goiter from man to animals by infecting the water supply of the latter with the feces of goiter sufferers. Having obtained only negative results in dogs, goats were selected for the experiment. These animals were from the same flock, between one and two years of age, of the female sex, and not pregnant. They came from a non-goitrous locality, and upon examination their thyroids showed no signs of hypertrophy. During a period of 108 days these animals drank only water which had been highly polluted with feces, at the end of which time the thyroid was distinctly larger than normal, and on microscopic examination exhibited an increase in size of vesicles, irregularity and thinning of their walls, and distention of vesicles with colloid. Goats fed on cultures of bacteria for the same length of time showed a tendency on the part of the thyroid gland to be smaller than normal, while the histological appearances were those of an active and very pronounced hyperplasia.

This diminution in size has been noted by other experimenters: Edmonds found in a partially thyroidectomized dog that the remaining lobe, although macroscopically smaller than normal, showed marked hyperplasia under microscopic examination. Farrant also concluded that the earliest stages of hyperplasia are associated with diminution in size rather than an increase.

**General Conclusions.**—I. We can accept as an established fact that the goiter causative factor, whatever its nature may be, is most frequently conveyed to the organism through drinking water.

II. The activity of the goiter causative factor is of an evanescent and fleeting character. It is destroyed by ebullition, materially diminished by filtration, and loses its goitrogenous power when exposed for a certain time to the air. The goitrogenous power of water allowed to stand in reservoirs is far more marked at the bottom of the body of water than at the top.

III. Heredity is an important factor in the etiology of goiter.

IV. Theories seeking to establish a correlation between certain geological formations and endemic goiter are no longer dependable. The same is true for the theories claiming that lime, magnesium, metal-

liferous rocks, chalk, etc., must be regarded as causative factors. Goiter is found in every latitude and in low as well as in high altitudes.

V. Although very clever, Repin's or the Plutonian Theory is purely hypothetical.

VI. There is no causal relation between radio-activity of certain waters and goiter.

VII. There seems to be enough evidence to show that goiter is not propagated by contact.

VIII. In view of the small proportion of persons affected and the higher percentage of females, the belief of some authors that goiter is due to a deficiency of iodine in certain geographic areas is hardly acceptable.

IX. The beneficial effect of iodine observed in the treatment of goiter is to be compared to the beneficial effect of mercury in the treatment of syphilis. Its inefficacy in the treatment of well-established goiters of colloid nature can be explained by assuming that the colloid state is due to the pathological influence upon the gland of the goiter-causative agent. When once established it becomes permanent. It is, so to speak, a by-product of the pathological activity of the gland caused by the goiter-causative factor.

X. So far the weight of evidence seems to be in favor of the "infection theory."

The occurrence of the disease in wild fish, its production in fish-cultural stations; its specific endemicity in certain definite regions and certain troughs of water; the experimental evidence as to its method of transmission; the efficacy of three well-known germicides in the treatment of the disease, iodine, mercury and arsenic; the influence of filtration upon the capability of water to produce goiter, and the destruction of the agent by boiling, all these arguments and others seem strongly to indicate that the cause of goiter is a living organism. The chances are that it belongs to the *trypanosoma* family. Chagas's thyroiditis is a very strong argument in favor of that viewpoint. Infection takes place through the water and soil. What is the nature of this infection, through what specific agent it takes place, is not known. Most probably, when the solution is obtained, the cause will be found to be within conditions which are quite subject to our control, as has been the case for malaria, yellow fever, etc.

## CHAPTER XVIII.

### MEDICAL TREATMENT OF SIMPLE GOITER.

TREATMENT of goiter may be *prophylactic, medicinal or surgical.*

**Prophylaxis.**—The best prophylaxis for goiter consists in avoiding the regions where goiter is endemic, and this is especially true for children living in endemic regions and whose parents have goiter. They certainly would be much better off if they could spend the first few years of their lives far from goitrigenous influences, as it is during this early period of their infancy that cretinism and other forms of hypothyroidism are apt to exert their greatest ravages. The well-to do women of Valais understood this a long time ago, since they not only used to spend all the time of their pregnancy in the “Mayens” of the Valesian Mountains, which were notoriously non-goitrigenous, but they also left their little offspring in these regions for the first year or two, because by so doing they learned empirically that the damages caused by the endemicity were considerably lessened.

In goitrous women living in endemic regions thyroid opotherapy should be undertaken from the beginning of the pregnancy and carried all the way through. It may not only benefit the mother by preventing, to a more or less extent, a compensatory hypertrophy of the thyroid due to pregnancy, but it may also prevent the little child from having a congenital goiter. Goitrous women living in endemic regions while nursing their babies should follow during all that time medical treatment with thyroid extract. In short, the same method of prophylactic measures employed to prevent the child from the consequences of a syphilitic infection of the father or mother, or of both together, should be applied to protect the little child from the consequences of endemic parental goiter.

If adults who are slightly affected with endemic goiter go and live in regions where endemic goiter is unknown, the chances are great that the goiter contracted in the endemic region will disappear. This has been often observed with young soldiers changing barracks, etc.

Hygienic conditions seem to be of importance in the prevention of goiter. It has been shown time and time again that the introduction and advance of hygienic conditions in places where goiter was extremely frequent, as the improvement in houses, food, clothing and in personal cleanliness, in drainage, and through the construction of roads, have

materially diminished the number of goiters or have entirely eliminated them. More than once it has been shown that entire villages or small portions of regions have been delivered from endemic goiter by providing a new source of water supply or by constructing water-tight canalizations and large reservoirs where water may be plentifully stored and aerated.

When one must live in a country where goiter is endemic the best prophylaxis for it is *boiling the water*. Filtering the water is not so effective. It has been shown experimentally that filtering the water through a Cumberland or Berkefeld filter, for instance, does not entirely protect against goiter.

### PROPHYLACTIC TREATMENT OF SIMPLE GOITER.

From the practical standpoint, the first instance of preventing goiter on a large scale was accidental and in connection with the sheep-raising industry in Michigan. Prior to the discovery of salt deposits around the Great Lakes, the future of the industry seemed hopeless, but with the development of the salt industry and with the use of salt by the sheep-growers, goiter rapidly decreased. The salt of this region contains appreciable quantities of both bromine and iodine, so that in places these elements are extracted on a commercial scale. The second instance of goiter prevention on a large scale was that carried out in certain brook trout. Some years ago the development of goiter in artificially raised members of the salmon family became alarming and many plants were abandoned on account of the disease. After considerable work, which led to the conclusion that the disease was, as had been surmised, simple goiter, the owners were able to completely prevent the disease in several hatcheries by the use of very small amounts of tincture of iodine added to the water. Later, the attempt was made to substitute whole sea fish for all or part of the diet, which proved to be, from the practical point of view, a cheaper and simpler method of complete prevention. Similar preventive work with farm stock is being carried out under Marine and Kimball's direction in some of the valleys of British Columbia, where goiter was so prevalent that farmers were unable to raise hogs, cattle, horses and chickens on account of myxedema (cretinism). Similar work in the prevention of goiter in hogs was recently reported by Smith. He was able to completely prevent fetal myxedema by the use of potassium iodide administered to the mothers during pregnancy.

Encouraged by these results and aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association, Marine and Kimball decided to apply the same plan of protection and treatment to the human species.



They chose as clinical material to work on school-children. 3872 school-girls of the 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th grades in the schools of Akron, Ohio, were examined and treated. The prophylactic treatment consisted in 0.2 of sodium iodide dissolved in 5 cc of water, given daily for ten consecutive days. The treatment in order to be effective must be given twice yearly, in the autumn and spring.

According to these authors, the most striking facts brought out in their examinations, is that, in the course of a year not a single pupil in whom the thyroid was normal, and who took the prophylactic treatment, showed a subsequent enlargement, while 15.9 per cent of those having a normal gland but who did not take the prophylactic treatment, showed thyroid hyperplasia. At the same time a distinct therapeutic effect was observed in those who had a moderate enlargement of the thyroid. This latter phenomenon was, of course, to be expected. Ill effects of the treatment were never noticed.

Kimball, Rogoff and Marine, in 1919, after examining again the girls (5th to 12th grades) in the public schools of Akron, Ohio, nineteen months after the beginning of their prophylactic use of iodine, did not find enlargement in previously normal cases, while 15.9 per cent of those not taking the prophylactic treatment were reported as having a definite enlargement. A distinct increase in the size of the slightly enlarged glands was noted in 38.1 per cent of the pupils using iodine, while only 27.8 per cent of those listed as not taking the treatment showed decrease in size.

The interesting feature of these experiments is that under the prophylactic treatment no new cases of goiter were developed in children who had previously normal thyroids, while 15.9 per cent of new cases occurred in children not taking the prophylactic treatment. The slight improvement observed in the ones having goiter and taking prophylactic treatment is in itself unimportant, since we know that iodine treatment under any form will in such cases bring about a few cures and a certain percentage of improvement. The only surprising thing is the low percentage of improvement in those taking the treatment (38.1 per cent) compared with the spontaneous improvement of those not taking it (27.8 per cent).

Judging from the results of experimentation by McCarrison, Messerli, etc., most likely other drugs than iodine could be used for prophylactic treatment, such as mercury, arsenic, thymol, etc. The results of such experiments bear very heavily upon the theory that goiter is due to deficient iodine in the body.

Be that as it may, Marine and Kimball are to be highly commended for their efforts. But before we raise our hopes too high we shall have to look for many more thousands of observations, prolonged over a period of at least ten years.

### MEDICAL TREATMENT OF GOITER.

A surgeon might think that, because all the goiters which come under his observation have more or less failed to respond to medical treatment, the latter is of no avail. This would be erroneous. As a matter of fact, a large proportion of goiters which are cured either spontaneously or by medical means never come under the observation of the surgeon. They have recovered under dietetic, hygienic and medical treatment. Medical treatment has its own field, and no conscientious surgeon will deny that there is a certain category of goiters which is purely medical. On the other hand, no learned and honest internist will refuse to admit that there is a class of goiters which is purely surgical. It would be indeed just as sad and blamable for a surgeon to advocate an operation for every thyroid hyperplasia seen, for instance, at the time of puberty, or during pregnancy, as it would be for an internist to treat systematically with thyroid extract, iodine or any other medicament, cystic or nodular colloid goiters. In everything there is a happy medium. Each form of treatment has its own indications and contraindications. There is no more sufficient reason to discard medical treatment because it has failed in a certain number of cases than there is to discard surgical treatment because a certain percentage of patients so treated died from operation.

**Indications for Medical Treatment.**—Medical treatment is especially successful in the parenchymatous forms of thyroid hyperplasia, seen at the time of puberty, pregnancy, and at the time of menopause. A diffuse colloid degeneration, when the latter is not too far advanced, may, too, be influenced by thyroid opotherapy or by iodine treatment. As a rule with nodular colloid or cystic goiter there is a concomitant, parenchymatous hypertrophy which must be regarded as an attempt by Nature to compensate the lost function of the degenerated portions of the thyroid gland. Such parenchymatous hypertrophy responds readily to iodine treatment and soon diminishes in volume, hence the belief of the public and the error made by many physicians that the colloid or cystic nodule has become smaller, when in fact it has retained the same size, but the gland *in toto* appears to be smaller because the parenchymatous hypertrophy alone has subsided. In conclusion we may say that medical treatment can be successful in all forms of parenchymatous hyperplasia such as that seen at the time of puberty, pregnancy, menopause, etc. If, however, the hyperplasia has gone too far the parenchyma does not return to its previous normal condition; hence the formation of a permanent goiter.

But medical treatment has its own limitations. In 1895, Bruns (“Beobachtungen und Untersuchungen über die Schilddrüsen-Behandlung

des Kropfes," *Beiträge zur klin. Chir.*, Bd. xvi, Heft 2) reported a series of 300 goiters treated by thyroid extract with the following results:

Complete cure . . . . .	8 per cent.
Marked improvement . . . . .	36 "
Slight improvement . . . . .	36 "
No improvement . . . . .	20 "

Three-fourths of the cases that improved relapsed.

**Contraindications to Medical Treatment.**—1. Medical treatment is useless in diffuse colloid, cystic, fibrous, calcareous and nodular goiters. It may, however, be valuable before operation by reducing to a minimum the concomitant compensatory hyperplasia which is often observed. This does not only facilitate the surgical act but also prevents the surgeon from removing, with the nodular goiter, a too great amount of glandular hyperplasia which would expose the patient to symptoms of hypothyroidism.

2. When diffuse colloid goiters have resisted an intelligent medical treatment for two or three months there is no need to insist any longer. Such cases must be turned over to the surgeon.

3. Every goiter causing pressure symptoms, especially every intra-thoracic goiter, since there is here little to be expected from medical treatment, must be treated by operation. The same is true of those goiters which produce cardiac symptoms.

4. Medical treatment is dangerous in those forms of goiter which grow rapidly; which become sensitive to pressure; which cause referred pains; which, in short, are suspicious of malignancy. In such cases, every day devoted to medical treatment means that much chance lost for a radical cure.

5. Medical treatment is useless in strumitis. In these cases the ideal treatment when possible, is to remove the affected lobe *en bloc* before peristrumitis has gone too far and before abscess formation and perforations have taken place. Otherwise, drainage must be resorted to.

**Medicaments.**—The medical treatment of goiter is as old as the history of goiter itself. The disease was one of those to which the most fantastic remedies of the Middle Ages were applied. Indeed, it was among the maladies supposedly healed by the King's touch. The Kings of England and the crowned and anointed Kings of France were thought to possess the power of curing certain diseases by touching the patient and by making the sign of the cross above them while pronouncing these words, "Le Roy te touche, Dieu te guerisse."

The touch of a dead hand was another popular remedy for goiter, and is mentioned as such by Pliny. It was thought that the goiter would disappear as soon as the dead body with which it had been brought in

contact became disintegrated by decomposition and decay. Peculiarly efficacious was thought to be the touch of a body killed by drowning or execution. A still more curious treatment consisted in enclosing a small living animal, such as a lizard or toad, in a sack and binding this upon the goiter, where the animal was allowed to die and thus was thought to carry off the disease in expiring. Amulets and loathsome remedies, such as excrements, etc., were among the recognized methods of treatment.

Very old and general is the belief in the influence of the different phases of the moon upon goiter, and it is still customary in the Ems Valley for the goiter patient to go out at night and gaze fixedly at the moon while holding his goiter with his right hand and repeating these words:

“Was ich sehe nehme zu (Let what I am looking at, grow).

Was ich fasse, nehme ab (Let what I grasp, get smaller).

Im Namen des Vaters des Sohnes und des Heiligen Geistes. Amen.”

Already in 1200 Roger von Salerno was using “toasted sponges,” toasted egg-shells and corals as treatment for goiter. When once it became known that the success of such treatment was due to the iodine content of these medicaments, it became logical, of course, to use iodine itself in goiter therapy.

**Iodine in Treatment of Goiter.**—It was the Swiss physician, Coindet, in 1829, who was the first to use *iodine* as a therapeutic measure against goiter. Since then it has become of daily use, and in fact it is still today the only specific treatment we have for simple goiter. We may say that medical treatment of simple goiter is contained in this one word: iodine. Thyroid opotherapy has proved to be a valuable asset in the therapeutic treatment of goiter, but its success seems to be in direct proportion to the iodine content of the thyroid extract.

That iodine influences goiter is a fact which is empirically very well established. But why does it, and how? The answer to the question is not yet at hand. So far as I, who believe that goiter is caused by an infectious agent, most likely of the trypanosomes family, am personally concerned, I regard the action of iodine upon thyroid hyperplasia as very similar to that of iodine, mercury and arsenic upon the syphilitic virus.

Up to date iodine has been used mostly under the form of iodide of potassium or sodium. It may be used externally or internally. For internal use the saturated solution of KI is best suited. Ten to fifteen drops a day will be amply sufficient.

Externally iodine may be applied, before going to bed at night, on the cervical region under the form of an ointment which is gently rubbed in for about 5 to 10 minutes, and the neck then covered with a flannel cloth. I advise rubbing the medicament over the cervical region purely



from a psychological standpoint. Patients are more apt to follow the treatment faithfully if they think that the medicine prescribed attacks the goiter directly. In fact, it does not matter what part of the body is rubbed, provided that iodine is absorbed in some way or another.

R—Kal. iodat. . . . .	10 grams
Aq. dest. . . . .	10 “
Lanolin . . . . .	30 “
Vaseline . . . . .	70 “
M. D. S.—For friction.	

Iodine under the form of *syrup of iodide of iron* may give, too, good results and especially as a prophylactic measure during pregnancy, puberty, etc.

Painting with iodine should be entirely discarded, as it blisters the skin and soon prevents the continuation of the treatment. Furthermore, it is a dirty therapeutic measure which has no special advantage, and which can easily be replaced by any one of the above-described forms and methods.

When thyroid opotherapy is adopted for treatment small doses should be used, for instance, one tablet of 5 grains every day. It is far better to administer small doses for a longer period than large doses over a short period. With such method one is less apt to have symptoms of intoxication, and, furthermore, the treatment may be protracted long enough until the goiter has entirely subsided. The chances for permanent results are better, too. It should, however, always be borne in mind that many of these thyroid preparations are perfectly inert on account of some faulty process in their manufacture.

Whatever form of treatment is adopted, the physician should always remember that it is not necessary to give large doses of any one of the medicaments used for goiter treatment, but that *small* doses are just as effective, and far less dangerous.

Plummer claims good results in the treatment with thyroxin of non-toxic vascular diffuse colloid goiters. Each lateral lobe may be as large as a good-sized fist. The thyroid arteries are distended and roll under the finger like a large lead-pencil; bruit and loud thrill are present, and in the majority of cases the basal metabolism is from 8 to 15 per cent below the average normal. In from twelve to twenty-four hours following the administration of thyroxin the thyroid vessels are not palpable and the bruit and thrill are no longer audible. The gland rapidly shrinks in size, in some instances becoming barely palpable in three weeks. The continuous administration of thyroxin prevents the reappearance of the goiter; however, on withdrawal of the drug the thyroid may rapidly attain its original size. After absorption of the colloid, iodine in many instances at least will prevent its redeposition.

The researches of McCarrison and Messerli are too interesting to be overlooked, as may be seen in the chapter on "Etiology of Endemic Goiter and Cretinism." Accordingly, intestinal disinfection should be undertaken in conjunction with the iodine medication. Mild laxatives and intestinal disinfectants should be prescribed daily during the whole period of treatment. Thymol, salol, creosote, etc., may be used. I give preference to salol and creosote, since thymol, when an acid-free diet is not observed, is apt to cause intense burning sensations in the stomach.

The relation between the thyroid and all the other organs of internal secretion has suggested the attempt to add to thyroid opotherapy the extracts of other endocrine glands. The results so far have not been very encouraging.

X-rays in simple goiter have not given satisfactory results.

**Crotti's Formula for Treatment of Non-toxic Parenchymatous Goiter.**—In the last few years I have been using the following formula in conjunction with the ointment:

R <sub>y</sub> —Sodium arsenate . . . . .	0.001 gram
Potassium iodide . . . . .	0.06 "
Sodium phosphate . . . . .	0.2 "
Thyroprotein . . . . .	0.02 "
Salol . . . . .	0.2 "

(Chocolate coated.)

D. S.—One tablet three times a day on empty stomach.

These compressed tablets are easy to take, are well tolerated, and usually do not cause symptoms of intoxication. I shall be glad to have anyone who gives them a trial report to me as to their efficacy and tolerance. They were prepared for me by Parke, Davis & Co., Detroit, Michigan. I have no objection to having any other reputable firm prepare them. I call them *simple goiter tablets*. It is not a patent medicine.

Whatever form of medical treatment is employed the patient and the physician must be prepared to see relapses of the goiter quite frequently.

**Dangers of Iodine Medication.**—Iodine given during too long a period of time, or in too large doses, not only produces the classical symptoms of intolerance, such as salivation, watering of the eyes, and congestion of the nasopharyngeal mucous membrane, but may also give rise to the worst thyrotoxic symptoms so similar to those seen in Basedow's disease that they have been called by Breuer, "Iodine-Basedow." (See the chapter on "Iodine-Basedow.") Every surgeon who has had some experience in goiter surgery has seen, I am sure, more than once these artificially produced cases of Graves's disease caused simply by an untimely, exaggerated and unintelligent treatment with iodine or its compounds. It

should be borne in mind that iodine treatment for goiter does not need to be prolonged over a very long period of time, nor does it need to be intense in order to be successful. When iodine is going to be active, it shows its efficacy very soon, say, after a period of a few weeks. Consequently, if after a treatment of two or three months with *small* doses of the medicament, no, or very little, improvement has been obtained, the medical treatment should be stopped. When successful, the treatment, for safety's sake, ought to be interrupted by small periods of rest of a few weeks in order to avoid symptoms of intoxication. We must not forget that there are patients who react so intensely to small amounts of iodine that not only do the worst symptoms of intoxication follow, but the goiter itself, instead of getting smaller, increases in size. There are people, too, who are so extremely sensitive to iodine that a simple sojourn at the seashore, or the use of certain mineral waters, is sufficient to cause in them marked thyrotoxic symptoms. It should be always remembered that there are goiters which are *latent Basedow goiters*, in which iodine medication is apt to start the "unhinging of the thyroid mechanism," whose consequences no one can foresee.

There is, too, a class of patients to whom the iodine treatment must be administered with great care and under the constant supervision of a physician. They are patients whose goiters are complicated with thyrotoxicosis, with a chronically inflamed respiratory apparatus, or goiters which are manifestly functionally insufficient. Medical treatment must be, too, carefully watched in patients with obesity, myocarditis, diabetes and nephritis.

### TREATMENT OF THYROID INSUFFICIENCY.

The treatment of thyroid insufficiency may be *medical* or *surgical*. The first method includes *thyroid opotherapy*; the second, *grafting*.

**Thyroid Opotherapy.**—Modern opotherapy took birth the day Brown-Séquard announced his theories on internal secretion. Already in 1869 that great physiologist had expressed the opinion that all the glands of the organism, with or without excretory canals, throw into the blood active and useful principles whose absence is detrimental to the organism. From that day the basis of scientific *opotherapy* was laid.

Theoretically, opotherapy aims to give back to the organism the natural products of the secretion of a gland whose function is absent or has become insufficient or perverted. In order to be efficacious, these products must consequently be qualitatively and quantitatively similar to the ones secreted normally. Practically, these conditions have not yet been obtained. Inasmuch as our organism is the laboratory where the most complicated, most varied, and the most delicate chemi-

cal metabolic reactions take place, it follows that only an accurate knowledge of these processes will enable us to undertake rational and successful therapeutic measures. This problem is the one which the study of internal secretion is trying to solve. The farmer of today does not farm his land in the same blind, empirical fashion as formerly, but requires the aid of the chemical laboratory in order to know which of the chemical constituents of the soil are deficient and which are not. He then treats the soil accordingly. In the same way, the future physician will be able to call into play the numerous isolated products of the organs of internal secretion as a therapeutic means against a great many pathological conditions. In a great many other conditions he will use chemical products which will prove themselves specific for these conditions, as has "606," for instance. That day will indeed be a great day which will see the future physician, instead of medicaments whose action is problematical, and at any rate empirical, employing this or that compound isolated from the organs of internal secretion or some other specific product, and by their clever use restore to normal a disturbed metabolism. Certainly, the future of internal medicine rests with and belongs to *Biological Chemistry*.

**Dangers of Thyroid Opothrapy.**—In fact, from the beginning of opotherapy it has been observed that in animals as well as human beings, thyroid preparations were liable to cause symptoms of intoxication. Bouchard reported headache, irritability, muscular and articular pains. Murray saw after the administration of thyroid preparations, nausea, vomiting and loss of consciousness. Stabel saw a patient, who had been taking a thyroid preparation as an antifat, become delirious and die. Béchère saw similar cases and considered thyroid products as cardiac poisons. In a myxedematous patient, after ingestion of 92 gms. of thyroid extract, he saw a marked tachycardia, tremor, exophthalmos, rise in temperature, and increased perspiration. Symptoms of hyperthyroidism have been frequently noticed in connection with opotherapy. One of the most striking cases is the one reported by Nothaft. A man in good health in order to reduce obesity undertook, on his own initiative, to take in a few weeks a thousand thyroid tablets of 5 grains each. He developed a typical Basedow's disease, with goiter, exophthalmos, tremor, increased perspiration, loss of flesh and glycosuria. The medication was stopped and ten months after the patient was normal again. Ferrarini reported the case of a woman who took thyroid as an antifat cure, 6 to 8 tablets a day. In two months she lost 8 kilos in weight and complained of vertigo, palpitation and insomnia. Nevertheless, she increased the quantity of thyroid and soon began to get nervous, with pulse 150, diarrhea and constipation, psychic trouble and hallucinations. Boynet reported the case of a student who, during eight days,



absorbed six to eight sheep thyroids daily. He soon developed a swelling in the thyroid, palpitations, tremor and an extremely advanced delirious condition which subsided only after the medication had been entirely discarded. My friend Gagnebin, while a medical student, submitted himself to a series of experiments in order to determine the action of the thyroid on the normal organism. For a period of about two weeks he absorbed daily one lobe of the thyroid of a sheep. At the end of that time the palpitations had become violent, while fever and abundant sweating were present. The tremor was so intense that he could not raise nor even carry his food to his mouth, while exophthalmos had become very marked. The experiment was interrupted and all the symptoms gradually disappeared. This toxicity of the thyroid products has been confirmed by almost everyone who has resorted to thyroid opotherapy. Gregor, however, seems to have been more fortunate, since he never met with toxic accidents in cases where enormous doses were given, such as 45 grains daily. Usually, however, the symptomatology was found to be very much the same: nervous troubles, characterized by irritability, insomnia, vertigo and headache; digestive troubles characterized by nausea, vomiting, diarrhea and constipation; cardiovascular disturbances characterized by tachycardia; and increased vascularization of the thyroid have been most frequently observed.

Thyroid intoxication seems to center its effects mostly on the cardiac, nervous and gastro-intestinal systems. Intoxication is due to the medicament itself just as it is seen in any other medicament when given in too large or too prolonged doses, as, for example, strychnine, digitalis, etc. As antifat, thyroid products must be used with the greatest circumspection, as accidents of collapse of the gravest character may occur. Always bear in mind that myocarditis is a very frequent corollary of obesity.

A part of the toxic symptoms following thyroid opotherapy are certainly due to absorption of putrefied products which, according to Lang and Gregor, occur rapidly in the thyroid. They may be partly due to choline, to methylamine, to products of autolysis and to the presence of toxic lipoids. This is corroborated by the fact that ingestion of fresh thyroids does not cause such toxic symptoms. Ghedini claims that the same toxic symptoms may occur with the pancreas, thymus, etc. Recently, Chamagne has found that thyroids in a fresh state are dangerous in proportion to the time which has elapsed since their removal; their maximum of toxicity is to be found between the fifth and sixth days. If the thyroid is deprived of its lipoids, its toxicity is considerably reduced.

In conclusion we may say that the thyroid's toxicity is partly due to its lipoids, which are very labile, and to the products of autolysis;

as we know, the toxicity of an organ is in proportion to the lability of its lipoids. Some of the other symptoms, as cutaneous eruptions, muscular and articular pains, must be referred to the introduction into the organism of albuminoid substances of animal origin. The remaining group of symptoms, however, must be put in relation with the absorption of thyroid extract. They constitute what we call *thyroidism* and are characterized by tachycardia, headache, vertigo, mental excitation, tremor, dyspnea, fever, protrusion of the eyes, polyuria, glycosuria, albuminuria, polyphagia, polydipsia, loss of flesh, etc. Thyroidism of a moderate degree is very frequently associated with simple goiter. In exophthalmic goiter, however, it may acquire great intensity.

**Ingestion Method of Treatment.**—After a long period of experiments and trials it is now universally admitted that the *ingestion method* is the easiest and most effective treatment in thyroid insufficiency. *Intravenous* and *subcutaneous* injections have been entirely discarded, as they are dangerous and do not offer any advantage over the ingestion method. Subcutaneous injections are not only dangerous because the thyroid products are not sterile, but also because they determine severe symptoms of *anaphylaxis*. Rectal feeding, although less effective than feeding by mouth, may be employed in certain conditions when it is necessary to spare the gastro-intestinal tract.

Medical treatment should be started with small doses and must be pursued with extreme care and vigilance. In this way symptoms of intoxication, such as vertigo, sensation of heat, headache, etc., may be spared to the patient, and, furthermore, this method gives him time to get used to the medication. It has the further advantage of determining the dose which is necessary for each given case to be therapeutically effective and not to be harmful. Even in myxedematous patients where *a priori* it would seem logical to administer large doses on account of the suppressed thyroid function, one will meet with disappointments and failures if treatment is not started with great prudence and judgment. *A fortiori*, this will be true in cases of partial thyroid insufficiency only. In such conditions we have no means of knowing how much medication will have to be given in order to obtain good therapeutic results, hence again the necessity of starting the medication with small doses. Furthermore, we should always bear in mind the possibility of idiosyncrasy. With thyroid, just as well as with other medications, the most severe intoxications have been known to follow the administration of very small doses of thyroid extract. The cause of these side actions is not known, but it has been suggested that during the course of myxedema, certain substances may accumulate in the organism and that these substances may be broken down by the thyroid in a manner analogous to the liberation of endotoxins when pathogenic bacteria are

destroyed in large numbers in the body during the course of treatment of an infectious disease.

In the treatment of thyroid insufficiency, what are the glandular preparations to which we should give preference? Theoretically, the *fresh gland* taken soon after the animal is killed, seems to be the ideal preparation, yet, such is not the case; first, because there is great difficulty in obtaining fresh thyroids just when they are needed; second, because fresh thyroids undergo putrefaction very rapidly and consequently are liable to cause the worst symptoms of intoxication. Furthermore, since the therapeutic activity of the thyroid varies with every animal, and in the same kind of animal varies with many conditions, the mixture of a great number of thyroid glands together is more likely to give a more uniform standard of activity. These requirements are met in the dried substance, providing it has been modified in the least possible degree and has not undergone putrefaction.

The *powdered desiccated thyroid* is a yellowish, amorphous, odorless powder, putrefaction of which readily betrays itself by a very unpleasant odor. When the latter condition is present the medicament must be discarded at once. The gland is official as "Desiccated Thyroid Gland," U. S. P. Powdered desiccated thyroid is best given under the form of a "cachet" or "wafer" in whatever dose thought necessary. We must only remember that the powder represents about five times its weight of fresh gland, consequently, 5 milligrams, 25 milligrams and 10 centigrams represent  $2\frac{1}{2}$ ,  $12\frac{1}{2}$  and 50 centigrams respectively of fresh thyroid. To insure greater uniformity it is suggested that the powder be required to yield from 0.17 to 0.23 per cent of iodine in thyroid combination. It is best to start with one dose of 10 to 25 milligrams of powder every other day at first, then every day, and then to increase the dose to what is deemed necessary.

It is to the credit of Burroughs-Wellcome & Co., Merck, of Darmstadt, Parke, Davis & Co., Armour, etc., to have put on the market a thyroid extract, prepared with the greatest care, in *tabloid form*. These tabloids contain from 0.1 to 0.3 gm. of dried substance. Their iodine content has been carefully tabulated. It is well to begin the treatment with one tablet in order to try out the susceptibility of the patient to the medication and then gradually to increase the dose until the most effective therapeutic effect is obtained. Children may encounter great difficulty in swallowing such tablets, and in that case it is better to prescribe the thyroid extract in liquid form. The *thyroid elixir* of the firm, Allen & Hanbury, of London, is useful in such conditions. One teaspoonful represents 0.1 centigram of thyroid.

The results of Plummer, who has used *thyroxin* in myxedematous cases, have been striking. He has injected at one dose 7 to 10 mgm.

intravenously with the most marked reduction in myxedematous symptoms in three or four days. However, the full effect of this dose does not occur for three or four weeks. The results have been further studied by obtaining the basal metabolic rate, which is often minus 40 to minus 50, and can be reduced to minus 20 or minus 10 by this single injection. Plummer asserts that 1 mgm. of thyroxin will raise the metabolic rate 2 per cent and that in choosing the proper thyroid extract one must keep in mind the fact that glands obtained in the winter months have less thyroxin and also less iodine. Another important fact, to quote from Kendall, is the state of preservation of the thyroid proteins. He says that the active principle of the thyroid contains two carboxyl and one amino group, and that bacteria may cause decarboxylation and deamination and so render physiologically inactive a thyroid extract, the iodine content of which will not be altered.

Since the general determination of the basal metabolic rate, it is possible fairly accurately to determine the proper dosage of thyroxin to keep an individual at the approximate normal.

Whatever form of thyroid medication is adopted, it is well to interrupt the opotherapy one week out of four. When the results are as complete as can be expected, a dose of "*maintenance*" should be kept up, two or three tablets a week, for instance, otherwise hypothyroidism is bound to relapse.

*Arsenic* is a very good adjuvant in thyroid opotherapy. Hertoghe claims that the thyroid medication is very much more active and better tolerated if the blood is alkalinized with *bicarbonate of soda*.

At first, on account of the marked degree of cachexia, one would be tempted to join to the thyroid medication a fortifying diet such as eggs, wine or meat, thereby hoping to ameliorate more rapidly the condition of the patient. Such views are erroneous. We have seen, in dealing with the experimental pathology of myxedema, that animals fed with a meat diet show much earlier and more severe symptoms than do those fed with a vegetable or milk diet. It is common knowledge that myxedematous cachexia in children appears, or becomes rapidly much more marked, at the weaning time, and especially at the time when an omnivorous diet is substituted for the milk diet.

We have seen, too, that in hypothyroidism the bodily temperature is invariably lowered: hence the indication to keep such patients in warm rooms, to avoid cold baths, and to prescribe warm ones instead, and warm fluids. Such adjuvants will materially increase the effect of thyroid medication.

Thyroid opotherapy must be used in every form of thyroid insufficiency, surgical and congenital athyroidism, spontaneous infantile and adult hypothyroidism, and in cretinism. The earlier the medication is



started the more brilliant will be the results. The medication in such conditions is specific and very often an absolute *restitutio ad integrum* takes place. It is remarkable to see how quickly the skin loses its myxedematous infiltration, its cyanotic character and becomes warm; and how the thick, fatty deposits in the neck, supraclavicular spaces and other regions of the body gradually disappear. The abdomen becomes smaller. Remarkable changes take place in the face not only because the myxedema retrocedes, but also because the intelligence of the patient awakes, and its apathetic condition disappears. Menstruation comes back and remains regular; the nutritional exchanges tend to become normal; the movements of the bowels become regular; temperature loses its subnormal character and oscillates between normal limits. In growing children the changes in the skeleton are remarkable. After a few months of treatment the bones grow remarkably and ossification takes place rapidly in the epiphyses as shown by the *x*-rays. It is not infrequent to find an increase of 8 to 10 cms. in the course of five or six months, even if the patient has reached the advanced age of twenty-five to thirty-five years. Unfortunately, however, the amelioration lasts only as long as the treatment is kept up.

*Opoththerapy in surgical athyroidism* or cachexia strumipriva or thyreopriva gives wonderful and rapid results. If accessory thyroid glands are present, they have time during thyroid medication to undergo compensatory hypertrophy, so that after a while they are able to supply the function of the lost thyroid. If cachexia is due to partial thyroidectomy, since thyroid insufficiency is not complete, the thyroid medication will at once restore the patient to his normal condition. Here, again, it will allow the remaining portion of the thyroid to undergo a secondary compensatory hypertrophy, so that after a few weeks or months the thyroid medication may be discarded because the physiological function of the thyroid has again become sufficient.

In *congenital athyroidism* and *spontaneous infantile hypothyroidism* thyroid opoththerapy is of great value. The earlier the opoththerapy is started, the more successful will be the results. When nanism and idiocy have acquired a marked development, the cure can hardly be expected to be complete; nevertheless, under treatment the changes are marvelous. There is a marked contrast between the child before treatment and the same one after a period of medication. Such patients regain their energy, enjoy every minute of the day a constant muscular activity which contrasts markedly with their previous apathy and marasmus. Furthermore, they are conscious of no fatigue, hence the danger of acute cardiac dilatation and collapse, and hence the obligation to watch these patients carefully. V. Robin reports the sudden deaths of two myxedematous children as the consequence of an exaggerated activity.

According to Bang, the thyroid principles are eliminated mostly through the milk secretion. If this is true, it might be advisable to prolong the nursing period as long as possible. Spolberini claims that a child nursed by a goitrous mother may develop hypothyroidism, and that this condition can be relieved at once if a new nurse is provided. Hence the indication always to examine the mother or the wet-nurse in every case of suspected thyroid insufficiency in the child.

In *spontaneous adult hypothyroidism* the results of opotherapy are equally good, but are not so persistent as in surgical hypothyroidism, because in the first condition, the chances for having accessory thyroid glands are remote. If they had been present, they would indeed have undergone a secondary compensatory hypertrophy during the time the thyroid was becoming insufficient, and would then amply supply the deficient secretion of the gland and thus prevent the development of hypothyroidism. Consequently if present, they were not "Funktions fähig" or functionally capable enough to supply the thyroid deficiency.

Systematic treatment of *endemic cretinism* is more of a social problem than a fight against each individual case. It is not only a humanitarian question, but it is also a very important economic problem. If we stop to think that in France alone there are 120,000 cretins, that other countries, as Switzerland, Italy, Austria, etc., are affected in about the same proportion, if not more, it will be easily understood why von Wagner, and Van Jauregg, of Vienna, have sought to have Austria furnish thyroid medication free of charge to its inhabitants.

Unfortunately, in endemic cretinism the results of opotherapy are not as good as in other forms of hypothyroidism. Von Wagner, Magnus-Levi, Weygandt, Gauthier and others claim to have had good results, but others, as Bircher, Scholz, Kutschera, etc., say that thyroid opotherapy has no influence upon cretinism. At any rate we may say that the treatment of a well-established case of cretinism is more or less *hopeless*. Only in cases *where an early diagnosis is made* before the somatic symptoms have reached their development, and provided, that the cretin is transferred from the endemic region into another free from goiter and cretinism, and submitted to an intelligent thyroid treatment, can we hope to stop the development of the disease. In that way the pathological changes in the skeleton and in the organs of sense and in the intelligence may be prevented. In fully developed endemic cretinism, if opotherapy is beneficial, the somatic symptoms show improvement; the intellectual sphere, however, is seldom materially benefited. Cretins are so very sensitive to thyroid medication that they may show symptoms of thyroidism characterized by nausea, vomiting, fever, tachycardia, insomnia, and loss of flesh.

The best prophylactic measure against goiter and cretinism is to purify the drinking water, but *boiling the water* is the safest prophylaxis. In regions where goiter is endemic, cistern water offers a great deal more security than the ordinary drinking water. In regions where goiter is endemic people have remained absolutely free from goiter and cretinism by building cisterns and using this accumulated rain water instead of the ordinary water of the vicinity.

So far as endemic deaf and dumbness is concerned, the results of thyroid opotherapy have been negative. Every effort to teach these cretins, as is done in deaf-and-dumb asylums, has been a failure. However, Wagner thinks that if the modern methods employed in the asylums of deaf and dumb should be applied to these cretins, it would not be impossible to obtain some results, because he believes that the disturbances are peripheric, being caused by an abnormal development of adenoids which interfere with the Eustachian tube and thus cause secondary inflammation in the hearing apparatus. Schwendt and Wagner found pathological changes in the tympanic membrane and anomalies in the hammer. Wagner found a chronic middle-ear catarrh and Alexander found an atrophy of Corti's organ. On the other hand, Kocher and others believe that these disturbances are not of peripheric but of central origin, being localized in the cortical centers, and are of the same nature as auditive and sensorial aphasia. The peripheric hearing apparatus is able to transmit the impressions, but the central nervous apparatus is unable to register them.

In small thyroid insufficiency or fruste forms of hypothyroidism the results obtained by opotherapy have surpassed the greatest expectations. As we have seen, Hertoghe, Magnus-Levi, Gauthier, Thiberge and others have widened this field and recognize that hypothyroidism is the etiological factor of many pathological conditions which up to then had remained a blank for the medical profession.

**Conception and Hypothyroidism.**—Conception is to some extent dependent upon the adequate supply of thyroid substances in the organism. Montgomery has shown that pregnancy often follows thyroid feedings in hypothyroidal women.

**Polyglandular Treatment.**—On account of the functional correlation which exists between all endocrine glands, and on account of the influences which they exert one upon another, it is easily understood that every one of them must be in a state of unstable equilibrium, so that disturbances in one of them may have a more or less marked repercussion upon the other glands. By throwing into the blood compensatory or antagonistic products, these fellow-glands may be able to hold the physiological balance in its normal limits, but in other conditions, they may not succeed, hence the disturbances which may not be directly in

relation with thyroid insufficiency, but which are related to it only indirectly, viz., by disturbing the polyglandular equilibrium. Consequently, it may be rational in certain cases to add to the thyroid medication the opotherapy of the glands which seem physiologically at fault. Such indications will be the result only of a careful study of the symptoms seen in the patient and of a better knowledge of the function of endocrine glands.



## CHAPTER XIX.

### THYROID GRAFTING.

ALTHOUGH Schiff had shown long ago that transplanted thyroid was physiologically active, it was only in 1883 that Kocher and Bircher demonstrated its efficacy as a therapeutic measure, and since then it has been freely used by many other surgeons. Bircher was the first to transplant the human thyroid into the abdominal wall of a patient. The results were good but only temporary. One and one-half months after transplantation cachectic symptoms reappeared. He made a second grafting whose results were not permanent, although they lasted longer than in the first case. Lubarsch sought to transplant thyroid into the kidneys. Christiani advocated grafting small particles of thyroid into the subcutaneous tissues. His method is known as the "grafting en semis," and consists in burying small particles of thyroid, a little larger than a grain of rice, into the subcutaneous tissue. Each particle must be buried separately and as many as twenty-five to forty of these small particles may be placed in one sitting. Christiani was able to demonstrate histologically that twelve years after grafting, some of these small glandular particles were still alive, capable of function, and that the myxedematous symptoms had entirely disappeared. One of his cases which he published in collaboration with Scharrin is of great interest, as it shows that this method can be successful. A young girl, seventeen years old, had been completely thyroidectomized. As this patient was insufficiently benefited by opotherapy, Scharrin and Christiani made two series of "grafting en semis." The patient was greatly benefited. Two years after she became pregnant and gave birth to a *normal* child. Curiously enough, during pregnancy several of the implanted particles showed a temporary hypertrophy similar to the one seen in the thyroids of pregnant women. One of Kocher's patients who had been grafted with thyroid gland in the abdominal wall two years previously, developed a tumor which suppurated, and was then finally eliminated. Symptoms of hypothyroidism recurred at once.

Payr thought that the organ of choice for the transplantation of the thyroid was the spleen. The results in one of his cases were extremely brilliant. In a six-year-old child affected with congenital athyroidism, he transplanted into the spleen of the child a portion of the normal thyroid belonging to the mother. Five months after the little patient had grown 12 cm. Unfortunately, notwithstanding the close consanguinity of the "donor" with the "recipient," thus enhancing the chances of success for the taking of the graft, the results did not remain permanent, since after a certain period of time symptoms of thyroid insuffi-

ciency recurred. Müller and Moscovicz transplanted thyroids into the epiphysis with some good results. Kocher prefers the upper part of the shaft of the tibia, von Eiselsberg, the preperitoneal fat, as the place of election for the grafting of thyroid. Whatever method of grafting is chosen, too often the results are only temporary; the transplanted part undergoes a gradual resorption, so that after a certain time the transplanted thyroid develops vascular connection with the neighboring tissues and may then become permanent.

The solution of this problem was thought to have been found when Carrel related his wonderful experiments on vascular anastomosis. The promises of this method were great, yet deceptions only were in store. Although Carrel, Stich and Makkas, Borst and Enderlen were able in very few instances to report successful "autotransplantations," they invariably failed when they tried "heterotransplantations." In a series of experiments undertaken in that line, although every possible aseptic precaution was taken and the technic of vascular anastomosis mastered, I was never able to obtain permanent heterotransplantations. Invariably six to twelve weeks after every trace of the transplanted thyroid had more or less entirely disappeared; all that remained was a small mass of connective tissue. Microscopical studies show that at first there is a central necrosis taking place in the grafted lobe, the colloid substances diffusing through the surrounding structures. Furthermore, the lymphocytes and leukocytes collect about the graft; fibroblasts become very active and, finally, a mass of connective tissue is formed.

In 1914, Carrol Smith after a series of experiments came to the conclusion that:

1. Administration of iodide of potassium to a guinea-pig in which a piece of its own thyroid gland had been transplanted did not seem to have any marked effect on the behavior of the gland. He did not find atrophy of the gland, as reported by Christiani, after the use of thyroid tablets.

2. The thyroid gland shows early central necrosis. The peripheral acini only remain intact. Regeneration takes place by the growth of thyroid tissue from the peripheral acini toward the center. These findings agree with those of von Eiselsberg, Sultan, Christiani and Enderlen.

In conclusion, we may say that up to date the permanency of the results of thyroid grafting are in the great majority of cases doubtful; their immediate influence upon hypothyroidism, however, is brilliant, and is due to the resorption of the grafted thyroid tissue instead of its function.

The failure in obtaining successful heterotransplantation is most likely due to chemical differences in the blood serum and in the tissues of the donor and recipient. It is well known that precipitins, agglutinins and hemolysins are formed on injecting the blood of one animal into another of the same species. This is so true that at the present time, when

transfusion of blood is contemplated, the blood of both the donor and that of the recipient is tested for hemolysins. Possibly the success of heterotransplantation will be obtained when we shall have learned how to prepare both the donor and the recipient so as to render them both isobiochemical.

So far the usual methods of grafting are: the subcutaneous method of Christiani, or "grafting en semis," described above, and the one advocated by Kocher, namely, transplantation in the *spongiosa tibiæ*. Instead of making the graft subcutaneous I prefer to implant the thyroid in the preperitoneal space. However, it is best to combine all these methods whenever any grafting is undertaken. Furthermore, the grafts must be numerous, as many are bound not to "take."

Transplantation in the *spongiosa tibiæ* (Fig. 63) has given in the hands of Kocher excellent results. This region being near the epiphyseal line is very vascular; the lacunes are large and thin, and a hole large enough to receive the graft can easily be made. The graft lies there comfortably without undue pressure; however, the graft must be of the same size as the hole, so that *no dead space exists between the wall of the hole and the graft*. This is essential for success. Hemorrhage must be entirely stopped by packing before grafting. This is of the utmost importance, too, because if hemorrhage occurs the graft will not "take," or at least will be greatly endangered, because hemorrhage infiltrates the graft, becomes organized and finally gives rise to connective tissue, which will ultimately destroy the glandular graft.

The gland to be grafted must be well nourished and as active as possible. Kocher recommended the use of thyrotoxic gland whenever possible. If this is not possible he advised treating the "donor" some time beforehand with iodine in order to stimulate the thyroid. The graft is taken during thyroidectomy as soon as it is removed from the "donor," and must be at once, without loss of time, grafted in the little cavity prepared in the tibia (Fig. 63) of the "recipient." The rapidity of this transport is of great importance. The easiest way is to have the two patients on separate tables and while thyroidectomy is being performed to have an assistant prepare a small cavity in the tibia of the "recipient." The size of the graft must not exceed twice the size of a cherry-stone. Every trace of glandular capsule must be carefully removed because this capsule prevents the neoformation of vessels between the graft and the neighboring tissues. After the graft has been carefully placed in the cavity the periosteum and the skin are carefully sewed up separately. In order to obtain as complete a vacuum as possible it is safer before closing up the periosteum to create a small vent in order to allow air to escape.

It is highly probable that most of the unsuccessful graftings must be attributed to the poor general condition of the tissues receiving the

graft, especially the subcutaneous ones. How could it be otherwise? A glandular graft transplanted in a "milieu" or medium soaked with myxedema and poorly vascularized is bound to be not "viable." Hence, in my judgment, an indication of great importance: before grafting the patient should be submitted to an intense thyroid opotherapy in order to "demyxedematize" him as much as possible. When that is done grafting may be attempted and opotherapy kept up until the graft has presumably "taken."



FIG. 63.—Figure showing cavity in the spongiosa tibiæ for grafting of the thyroid.

However, despite every precaution, grafting of the thyroid will still remain uncertain because the graft is transplanted into new surroundings endowed with entirely different physiological properties. As said before, the solution of the problem lies in the discovery of means capable of modifying the serum of the donor or recipient, or both together, so as to render them closely similar chemically, *i. e.*, *isobiological*.

It must be said, however, that if the thyroxin, as isolated by Kendall, fulfils its promises, as it seems it will, grafting of the thyroid for thyroid insufficiency will become entirely obsolete.



## CHAPTER XX.

### INDICATIONS FOR OPERATION IN SIMPLE GOITER.

WE may say that thyroidectomy undertaken under correct indications and performed with good technic is practically without danger and must be undertaken:

1. In every case where medical treatment has failed.
2. In all colloid, fibrous, cystic goiters (Figs. 64-67).
3. In all diffuse colloid goiters which have resisted medical treatment.
4. In all goiters which are partially or totally intrathoracic.
5. In all goiters causing pressure symptoms on the trachea, esophagus, on the inferior laryngeal and sympathetic nerves, and on the arterial and venous trunks.
6. In all goiters having a tendency to produce a goiter-heart, be it mechanical or thyrotoxic.
7. All goiters causing unsightly deformities.
8. In all vascular goiters, thyrotoxic or not.
9. In all goiters secondarily complicated with symptoms of hyperthyroidism.
10. In all goiters which after a period of latency, especially at the time of menopause, suddenly begin to grow, show changes in consistency, lose their mobility, and cause referred pain. These goiters are suspicious of malignancy and should be treated by operation without delay, regardless of the patient's age.
11. Operation should be performed in all cases of strumitis. As I have said before, the ideal in such cases is to remove the infected lobe *en bloc* while pus is still well encapsulated and before peristrumitis has taken too great a development. If this is no longer possible, then the abscess should be lanced and drained.
12. As a general principle I would say: Do not wait too long before operating any one of the cases which have *become surgical*. The tendency of today's surgery is to be not only curative, but also to be prophylactic: we aim to operate before complications have occurred. In appendicitis, we do not wait until the abdomen is full of pus; we do not even wait until the appendix has ruptured. At the first symptom we open the abdomen and remove the appendix. In so doing we not only cure the patient of his present attack, but also, we operate before the condition has had time to become dangerous: we thus add prophylaxis

to cure. In our gall-bladder surgery, we do not wait until the patient has become so thoroughly poisoned by jaundice that the result of the



FIG. 64.—Nodular colloid goiter.



FIG. 65.—After the operation.

operation will be highly problematical. Nor do we wait until a gall-bladder empyema has perforated into the abdominal cavity or into a



FIG. 66.—Nodular colloid goiter involving both lobes and isthmus.



FIG. 67.—Ten days after operation.

neighboring organ before interfering surgically. At the first symptoms we intervene, because we have learned at the cost of too many lives that procrastination too often causes death, or failure to cure. There, too, the cure of the patient is no longer our sole object; we try to interfere before the situation has become serious. There, too, we add prophylaxis to cure. In our gynecological work we do not delay until ovarian or uterine tumors have reached a monstrous volume, until they become malignant, in short, until they have endangered the patient's life, before we advocate surgical treatment. As soon as these organs begin to show symptoms, we remove them. We do not only aim to cure the patient of her infirmity, but we also strive to operate while the chances are all on our side, hence again we have prophylaxis and cure in view. And so it must be in goiter surgery. Why wait until the goiter has reached an unsightly deformity, caused pressure symptoms, determined thyrotoxic symptoms, etc., before operating? Why even wait until it causes many symptoms at all? As long as the goiter *has become surgical*, the earlier the operation the better the results will be for everybody concerned, the patient and the surgeon. As we remove any tumor of the breast for fear of malignancy, no matter if that tumor gives symptoms or not, so I believe we should remove *any surgical goiter* for fear of mechanical symptoms, of the thyrotoxic symptoms, and for fear of malignancy. Here, too, prophylaxis goes hand in hand with cure. Of course I am speaking of the *surgical cases only*: whenever there is a chance for medical treatment it must be employed judiciously. One should use his best judgment, and should not allow his medical conscience to deviate in the slightest degree from the right path. Surgical therapeutics should not be applied indiscriminately. As in any other line, conscience, experience and knowledge are the best guides.

We should never forget that the extent of the surgical treatment must depend upon the nature of the goiter. It is not enough to diagnose a goiter, but we must go a step farther and must analyze its *functional capacity*. A hypo-active goiter will be treated entirely differently from a hyperactive one. Of course surgically it is an easy matter to even up a neck, to resect a parenchymatous goiter, or to enucleate a conglomeration of cystic or colloid nodules. From the esthetical and surgical point of view the operation is a success, yet a great deal of harm may have been done. Indeed, it is not so rare to find patients with large colloid goiters whose thyroid secretion is barely sufficient to meet the physiological purposes. In such conditions thyroidectomy may result only in aggravating the already existing hypothyroidism. To be sure, enucleation of the colloid or cystic nodules, in some of these patients, may help materially the function of the thyroid, since the pressure on the normal parts of the gland having been removed the normal paren-



chyma can expand and resume its physiological function, so that a complete *restitutio ad integrum* of its functional activity may follow.

All this goes to show that the question does not reduce itself simply to the removal of the enlarged gland no matter if this goiter secretes too much or too little. It is clear, too, that a correct interpretation and a correct therapeutic measure, whatever it may be, undertaken at the proper time and with judgment, may restore the normal functional equilibrium not only of the thyroid but also of the entire inner secretory apparatus.

The most difficult cases to handle are those in which, besides the colloid and cystic nodules, there is a marked compensatory parenchymatous hypertrophy. Should we in such cases decide to undertake an energetic medical treatment with iodine we may run the risk of increasing the functional activity of the thyroid and of throwing into the blood circulation an enormous amount of thyroid secretion and thereby determine what Kocher calls a "thyroid diarrhea," with all its thyrotoxic consequences. Should we, on the other hand, excise the degenerated portions of the gland we shall at the same time remove a more or less sizable portion of the compensatorily hypertrophied thyroid, and so possibly expose the patient to hypothyroidism. Such cases should be treated with the greatest care and handled, according to Kocher, (as we do, for example, suspected cases of syphilis); a trial treatment with very small doses of iodine should be given, and a careful watching of the patient should be instituted. The decision will be taken according to the results obtained.

### CONTRAINDICATIONS TO OPERATION.

Despite the most severe asepsis, and the most skilful technic, one runs the chance of losing his patient whenever the goiter has been of very long standing; whenever it has caused prolonged pressure symptoms, and whenever marked bronchopulmonary symptoms are present. The same dangers exist when goiter has caused marked cardiac disturbances, as myocarditis, dilatation of the heart, increased cardiac action, in short, whenever there is a mechanical or thyrotoxic goiter-heart. In these instances cyanosis of the face, edema of the hands and feet, even ascites may be present. In Basedowified goiters, where thyrotoxicosis has reached an advanced degree, the chances for fatal results have become greatly increased. The same is true of malignant goiters that have involved the neighboring tissues, especially the trachea and venous trunks. The same is true in strumitis when it has caused such a peristrumitis so as to involve the neighboring tissues in a similar manner as does the malignant goiter. In all these cases not only the results *quoad*

*vitam*, but also the immediate results are problematic. For one success, how many failures? In all such cases one must rely upon judgment and experience as the best guides.

### TREATMENT WITH INJECTIONS.

I think it can be safely said that punctures with aspirating needles and injections of medicinal substances in goiter are things of the past. This method of treatment is a blind, uncertain and dangerous one. The only instances in which I think it is justified are in inoperable cases of exophthalmic goiter, for which Porter advised the injection of boiling water. The treatment of goiter by the injection method is not new; almost every known medicament as ergotine, chromic acid, osmic acid, permanganate of potash, strychnine, Fowler's solution, liquor sesquichlorati, carbolic acid, tincture of iodine, ether, iodoform, glycerine solution, etc., has been given a trial. The injection of such substances is expected to produce a local sclerosis and finally to reduce the size of the goiter. It is injected directly into the parenchyma with a small syringe. Of course before injecting, aspiration should be made in order to see if the needle has penetrated a vein, in which case the position of the needle must be changed. These injections are repeated as often as necessary. After a few months of similar treatment, in many instances the thyroid shrinks in size, but in many others it does not, or it does so very irregularly. It is this that makes the method uncertain. Furthermore, the method is a dangerous one because hemorrhages and abscesses have been known to follow quite frequently. Sudden dyspnea after such injections has been often reported. Diffuse infiltration of the neighboring tissues has been noticed more than once. A great risk lies in the possibility of injecting the medicament into a vein. Horsley has shown that the injection of 15 cc of tincture of iodine into the jugular vein of a dog caused death.

One of the greatest disadvantages of this method is that it converts the thyroid into a fibrous mass which afterward not infrequently causes more trouble than the goiter itself. And then, finally, when the patient resorts to an operation, the surgical act is rendered extremely difficult on account of the fibrous degeneration of the goiter and its intimate adhesions with the trachea and other tissues.

All these inconveniences might be, however, overlooked if a danger far more serious were not hanging over the patient's head. I have in mind *sudden death*. This is not a matter of mere conjecture. Heymann reported 12 cases of death, and Wölfler, in 1891, reported 12 other cases. Death occurred either, because of sudden asphyxia due to the swelling of the goiter on account of hemorrhage or, because of strumitis. The case

of Bonnet reported by Vallette will serve as a good illustration of the danger of injections. Bonnet, a prominent surgeon of Lyon, was one day consulted by a young, handsome lady for goiter. It was a cyst which did not cause any disturbance whatsoever, but greatly distressed the patient from an esthetic point of view. She wanted to get rid of the tumor without operation and insisted upon having the treatment done by the injection method. Tincture of iodine was used. Everything went all right the two following days, so that the surgeon felt safe in leaving the patient and in going to the country. Three days after Bonnet returned. From the station he went straight to the patient's house to see how everything was getting on. To his horror he found a coffin surrounded by candles. What had occurred is easily told: necrosis of the goiter had taken place, strumitis had followed, and suffocation had occurred so rapidly that death ensued before surgical help could be secured.





# THYROTOXICOSIS.

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THIS condition is known, too, as *Graves's Disease*, *Basedow's Disease* and *Exophthalmic Goiter*. Mayo calls it *hyperthyroidism*, Kocher called it *thyrotoxicosis*. Following Kocher, I have adopted the latter denomination. My discussion, however, will have due regard for the classical terminology so firmly fixed in the literature that the usual names may be employed indiscriminately.

**History.**—That the Romans already knew something about exophthalmic goiter is shown by the fact that any contract for buying or selling of slaves was *ipso facto* invalidated whenever exophthalmos was present. The Romans may not have understood the thyrotoxic symptom-complex as a whole, but they at least realized that there was a direct relation between exophthalmos and a more or less marked physical incapacity. They learned by experience that a slave with exophthalmos was depreciated, disabled, inadequate. It was, however, not until 1780 that Flajani began to suspect that exophthalmos was only a symptom of a disease which he recognized and described, hence the name *Morbo de Flajani* given by the Italians to thyrotoxicosis. Later, Perry, in 1786, came to the same conclusions. It is, however, to Graves, in 1835, and to von Basedow, in 1843, that the honor must be awarded for giving a complete description of the condition. Since that time very little has been added to their clinical descriptions of the disease. The gains made since concern mostly the etiology, the pathology, and the treatment of that condition.

**Graves's Disease** is a condition characterized by a symptom-complex in which *cardiovascular symptoms*, *thyroid hypertrophy*, *exophthalmos*, and *tremor* are the predominating factors; these are called the cardinal symptoms of the disease. They are not always all present at the same time, nor are they all developed with the same degree of intensity; one or more of them may stand out more prominently than the others; one or more of them may be entirely absent. These cardinal symptoms are usually accompanied by a number of less important ones which, considered separately, seem to be of minor importance, but when grouped together acquire a strong diagnostic value.

## CHAPTER XXI.

### CARDIOVASCULAR SYMPTOMS.

CARDIOVASCULAR symptoms in Basedow's disease are certainly among the most important. There is no case of truly active Graves's disease without cardiovascular disturbances. The Basedow patient suffers and dies because of his heart. Cardiovascular disturbances form a clinical symptom-complex which is called the *thyrotoxic goiter-heart*, in contradistinction to the *mechanical goiter-heart* which we have described in our study of simple goiter.

The most constant and typical of the cardiovascular symptoms seen in Graves's disease is *tachycardia*. This symptom never fails. It is characterized by a long-continued rapid action of the heart. The number of heart beats varies, of course, with the condition of the patient and with external as well as with internal influences, but is always abnormally high. The pulse is persistently rapid and remains so for weeks, months and even years with more or less marked remissions, which, however, are never such as to render the pulse normal. Even during sleep, if the pulse is taken gently in order not to awaken the patient, it is found high, possibly in the neighborhood of 95 or 100, but very often far more rapid. Under excitement, physical effort, or for no apparent reason at all, the number of cardiac beats may vary between wide limits; the pulse, for instance, will rise from 100 to 150, 180 and possibly 200 in a very short time. Sometimes the mere change of the patient from the lying to the standing position is sufficient to cause the pulse to increase materially. Tachycardia varies, of course, during the development of the disease, being at times more accelerated than at others. Sometimes morning and evening remissions are seen.

**Differential Diagnosis of Thyrotoxic Tachycardia.**—It can be truthfully said that tachycardia is a specific symptom of Graves's disease, and to a certain extent, may even be considered as pathognomonic of that condition. To be sure, a rapid heart action often accompanies the so-called *neuroses*.

Since patients suffering from Graves's disease usually show more or less marked nervous disturbances, one might be tempted at first to consider their tachycardia as caused by a neurosis, but time and repeated examinations will show the difference between a merely excited pulse and that of Graves's disease. A persistent, high pulse-rate while the patient is at rest in bed is rare in pure neurosis, and must be regarded as highly

suspicious of thyrotoxicosis. Those who are only nervous will show great variations in their well-being; they will ere long calm down and their pulse-rate will fall accordingly, whereas the Graves's pulse, even if it shows some variations, does not calm down in the same proportion as does the nervous one. Furthermore, the simply nervous pulse becomes almost normal during sleep. As Thomson says, "The Graves's pulse runs as fast or faster than in fever, by day and by night, and always in sleep, with less change at each counting over long periods than in any other complaint."

Tachycardia due to *inflammatory* or *organic changes* in the heart itself can be easily eliminated, since in Graves's disease the heart is, as a rule, functionally but not organically deranged. It is true, as we shall see later on, that often murmurs are detected over the orifices of the heart, but these murmurs are mostly functional and not organic.

A quick pulse may be noticed in *anemic and debilitated patients*: but in such conditions the pulse varies in rapidity mostly with physical exertion, and as soon as the patient has enjoyed rest his pulse-rate falls accordingly. The rapid pulse seen in all fevers and Bright's disease may be eliminated very easily if one takes the trouble to examine the patient. The quick pulse resulting from the abusive use of tea, coffee, tobacco, etc., will soon be given its real significance after a little observation.

Tachycardia in thyrotoxicosis cannot and should not be mistaken for *paroxystic tachycardia*, which is a striking entity by itself. As its name indicates, that form of tachycardia comes on by paroxysms with the utmost violence. For no apparent reason and during a period of absolute welfare, the patient suddenly feels his heart bounding in his chest, the pulse rising to 180 to 200 beats; the entire cardiac area trembles, yet neither anxiety nor pain is present, and scarcely any dyspnea. I have seen a case in which cyanosis was very marked. This spell may last from fifteen to twenty minutes, or a few hours, and with the same suddenness with which it began, the paroxysm ceases abruptly, and the pulse becomes normal again. Weeks or months may elapse before another spell comes on. Sometimes, however, these paroxysms may occur at much more frequent intervals and may be of longer duration; they may even last for days. Under such conditions the prognosis becomes dubious; organic changes take place in the heart, the cardiac lesions become uncompensated and terminate by complete cardiac disarray. Little is known about the etiology of the paroxystic tachycardia. Having noticed that this paroxystic tachycardia is sometimes accompanied by some other thyrotoxic symptoms, and thinking that between paroxystic tachycardia and disturbances of the genital apparatus, such as menstruation, menopause, etc., there was a direct relation, M. E.

Savini thought that paroxystic tachycardia could be caused by an overfunction of the thyroid, producing in turn an ovarian or testicular insufficiency. Hence his advice to use ovarian extract for women and testicular extract for men. In his experience the treatment proved to be successful. If thyroid extract was given the condition got worse, thus showing that paroxystic tachycardia might still be regarded as a symptom of hyperthyroidism. In my case, however, where the thyrotoxic symptoms were manifestly present, thyroidectomy failed to have any effect on the paroxystic tachycardia. That condition showed a progressive course and terminated in death two years later.

During the recent war a number of cases of paroxystic tachycardia were observed in soldiers after prolonged fatigue. It was found that if a soldier should swallow a large mouthful of firm foodstuff, as bread, meat, etc., and if this was done at the beginning of the spell, the paroxystic tachycardia would stop at once. The mouthful of bread should be large enough to oblige the patient to make strong efforts at deglutition. The idea is to excite the vagus nerve so as to counteract the action of the sympathetic.

After all causes of rapid heart action have been eliminated, one is then obliged to fall back upon tachycardia of thyrotoxic origin. This tachycardia is peculiar on account of its striking persistence, and may be considered as a pathognomonic symptom. No other form of tachycardia compares with it for long continuance.

**Hyperthyroidism and Irritable Heart.**—During the past great war the question of “irritable heart” and its relation to thyroid hyperfunction was a much debated one. And justly so, as the loss of efficiency and the number of men affected were quite considerable. Goodall basing his conclusions on the study of 2250 cases of irritable heart was much inclined to hold the thyroid responsible for a great many cases. And so did James Barr, White and Hernanan-Johnson. Because only 4 per cent of the 504 cases studied showed a moderate hyperplasia of the thyroid, Lewis held that the role played by the thyroid in the production of irritability of the heart was unimportant. But palpation of the thyroid is sometimes quite difficult when one is trying to figure out its exact size. How many times, at operation, are we not surprised to find a thyroid very much larger than expected, and how many times do we not unexpectedly find, too, that an apparently small thyroid sends inwardly, between or behind the trachea and esophagus, good-sized portions of thyroid tissue. Consequently, palpation is not enough of a criterion when it comes to judge hyperfunction of a thyroid. Let us not forget that we find cases of thyrotoxicosis with no macroscopical enlargement of the thyroid.

It is fair to add that a certain number of his men were tested by Lewis with thyroid extract.



Harlow Brooks and Smith, on the other hand, attributed to the thyroid a great amount of responsibility for the production of the irritable heart while Friedländer and Freyhoff took the opposite view.

There can be no doubt that when such patients are tested with the varied laboratory methods which we have at hand today, a great many of those cases will be recognized as thyrotoxic, while others will fall into that class best classified as sympathetictonic, both conditions being closely allied. Some cases, however, do not fit into these two classifications.

**Etiological Explanation of Tachycardia.**—Tachycardia is the result of an increased susceptibility of the acceleratory as well as of the inhibitory system of the heart and of the diminished tonus of the peripheral vascular system, thus causing a vasodilatation. Inasmuch as irritation of the depressor nerve causes a marked dilatation of the bloodvessels of the thyroid, and since in turn the thyroid secretion, as shown by Asher and Flack, acts as an excitant of the same depressor nerve, we have here a vicious circle: the increased blood supply increases the thyroid function, and the increased thyroid function increases the blood supply through the action of the depressor nerve and influences the acceleratory as well as the inhibitory system.

**Palpitation.**—Palpitation is one of the most distressing symptoms experienced by the patient. Not infrequently it is the only symptom which drives the patient to seek medical aid. Palpitation is a symptom quite different from tachycardia, and should not be confused with it. No normal individual is conscious of his cardiac action; as soon, however, as he becomes aware of it, in other words, as soon as he feels that he has a heart, we say that he is suffering from palpitation: he is becoming conscious of his tachycardia. It would be erroneous to believe that the symptom, palpitation, is in direct relation to the degree of tachycardia. A marked degree of tachycardia as in fever, for instance, may be present, yet the patient is not conscious of it as a rule; he does not complain of palpitation, whereas in other conditions where possibly a very moderate degree of tachycardia is present, the patient may be very greatly distressed by palpitation. He feels his heart bounding in his chest, beating irregularly and then rapidly, all in turns, and all without the slightest apparent cause. To be sure, this condition is made worse by excitement, physical exertion, intoxication, etc. Palpitation comes on mostly by spells and is especially frequent at night; it banishes sleep, and keeps the patient greatly distressed. Sometimes palpitation is dependent upon the position occupied by the patient in bed. For some patients it becomes more accentuated when lying on the left side, and more rarely so when lying on the back.

Palpitation and tachycardia may sometimes be accompanied by

pain in the cardiac region, which resembles very much the pain seen in *angina pectoris*; even loss of consciousness may occur. Ordinarily such spells, even when not accompanied by loss of consciousness, leave the patient in a state of complete prostration.

**Thyrotoxic Heart.**—In mild forms of Graves's disease the physical examination of the cardiac apparatus does not reveal any important pathological conditions. In fact, in the great majority of these cases this physical examination is negative. However, this is no longer true in advanced cases of hyperthyroidism. There the findings revealed by inspection, palpation, percussion, auscultation and *x*-rays may be quite marked.

Inspection shows that over the entire cardiac area the heart-beats are transmitted more or less violently to the anterior wall of the chest. Sometimes the entire thorax is shaken synchronously with the cardiac contractions.

The intensity of the heart action is, as a rule, increased. The heart is felt bounding in the chest; the entire thoracic region may be shaken by the intensity of the cardiac beat. Sometimes the cardiac impulse is so intense that the entire body is shaken synchronously with the heart-beat, especially when the patient lies quietly, or is in a sitting posture. In the latter position this is most evident in women, especially when wearing hats with feathers on them, the feathers then serving as an index. In such instances one can count the pulse, although at some distance from the patient. Murray and others claim to have heard the heart-beat at a distance of three or four feet from the patient's chest.

Palpation of the heart shows the presence of a *thrill* over the cardiac area. It shows, too, that the apex-beat in Graves's disease is usually forcible, sudden, bounding and rather diffuse, and a beat can be felt farther to the left without there being necessarily an increase in the actual cardiac outlines.

Percussion shows that the cardiac area may be greatly enlarged; in some instances the volume of the heart may attain very large dimensions, as is confirmed by the *x*-rays. The increased volume of the heart is caused chiefly by dilatation which may affect both chambers and auricles, but seems to predominate over the left heart. Of course a certain amount of concomitant hypertrophy may be present at the same time. Cardiac dilatation is not permanent, but retrocedes in direct proportion to the improvement of the patient's condition. This can be confirmed by repeated clinical as well as by roentgenographic examinations.

Auscultation often reveals the presence of a *murmur* which is mostly localized over the base of the heart and from there irradiates toward the other orifices. Its maximum of intensity is found generally over the pulmonary valve, and is systolic in character. Not infrequently such murmurs are so intense that they may be felt with the hand over the

cardiac area; they then form what is known as a *thrill*. These murmurs, when very marked, may at first give the impression that severe cardiac lesions are present, yet their localization at the base of the heart, and the rapidity with which they disappear, or at least ameliorate as the patient's condition improves, show that we have to deal not with organic but with functional disturbances. They seem to be mostly dependent upon the dilatation of the cardiac chambers, causing in turn an insufficiency of the cardiac valves. To be sure, organic cardiac disturbances may be present, but these cases are in the minority. Even a systolic murmur at the mitral valve accompanied by an accentuation of the second pulmonary tone does not necessarily mean that we have to deal with a mitral insufficiency.

X-rays are a very valuable adjunct in estimating the volume of the heart; they are far superior to any other means.

In Basedow's disease the cardiac fibers seem to be particularly weak and easily exhausted. The thyrotoxic poison, whatever it is, seems to have a special affinity for the cardiac muscular elements. This may possibly explain the cardiac dilatation so often met with in Graves's disease. That in the majority of the cases we have to deal with a dilatation instead of a cardiac hypertrophy is shown by the fact that after an operation, or after the process has been healed by some medical means, the limits of the heart have a tendency to return to normal. In some instances the cardiac dilatation may become acutely marked in a short time; it is then accompanied not only by murmurs over the entire cardiac area, but also by tricuspid insufficiency, venous pulse, congestion of the liver, spleen, kidneys, edema of the limbs, ascites, etc. It follows from Puesch's researches that in Basedow's disease, although the work of the heart *in toto* is manifestly increased, the systolic cardiac output is lower than in normal conditions. This latter fact might explain, too, the mode of origin of cardiac dilatation. Indeed, the muscular fibers being under the influence of the thyrotoxic poisons on the one hand, and the systolic output of blood being diminished on the other hand, it becomes impossible for the heart to expel from its chambers the amount of blood which has flowed into it, hence *dilatation*. To be sure, a certain amount of hypertrophy nearly always accompanies dilatation, yet this is not always the case, as instances are seen where before death an increased volume of the heart is present, and where after death postmortem reveals a small, contracted heart. These cases of cardiac dilatation without some degree of concomitant hypertrophy, in other words, the cases of non-compensated dilatation, have a very bad prognosis. Hypertrophy, when present, involves mostly the left ventricle; however, all the other chambers participate in a lesser degree with that hypertrophy.

Electrocardiographic studies of the heart show that in early cases of thyrotoxicosis, tachycardia is not usually accompanied by any signs of myocardial change. It is only in older cases that myocardial degeneration usually takes place. It is then characterized by any type of cardiac irregularity, sinus arrhythmia, premature contractions, auricular fibrillations, ventricular extrasystoles, etc. In a great many instances, after successful treatment, be it medical or surgical, the cardiac condition is much improved or even restored to normal.

**Myocardial Histological Pathology.**—Up to very recently the pathologists have been satisfied with a record of the gross appearance of the cardiac lesions; dilatation of the right chambers, moderate hypertrophy of the left ventricle, fatty degeneration, were about all that were observed. Microscopical examinations were reported to be mostly negative.

Fahr, in 1916, reported for the first time actual destructive lesions of the myocardium, consisting of interstitial myocarditis, the cardiac muscular fibers showing degenerative changes, and infiltration of leukocytes being present between the muscular fibers and especially around the bloodvessels. Furthermore, fatty and hyaline degeneration were noticed.

In 1921, Goodpasture reported 2 cases of acute necrosis of the myocardium in exophthalmic goiter. He observed marked interstitial edema of the myocardium with focal necrosis of the ventricles, and especially of the auricles. The most characteristic lesion found histologically was the disintegration of the cells, the regular striations having disappeared and hyaline degeneration being quite marked. A number of mononuclear phagocytes were present. Fatty degeneration was almost totally absent.

Myocardial necrosis may be acute or chronic. It may be caused either by an infarctus, by an infection, or may be the result of a toxic condition. In the first case it is due to occlusion of a terminal artery; in the second case it is associated with a severe infection caused by staphylococcus, streptococcus, or any other bacilli. In the third instance, microbes are not directly responsible but their toxin affects directly the myocardial cells. In thyrotoxicosis, one is confronted with the question whether myocardial necrosis is a direct result of thyroid intoxication or the result of myocardial exhaustion, or whether they are purely accidental. Considering the fact that clinical cardiac disturbances are always present in true thyrotoxic goiter, and that when thyrotoxicosis is of long standing, marked cardiac changes take place, one is rather justified in assuming that the primary cause of these myocardial necroses is of thyrotoxic origin. Other factors, of course, may supervene, such as preëxisting cardiac lesions, cardiac exhaustion, etc.

**Thyrotoxic Pulse.**—Sphygmographic curves of the Graves's pulse show that it has all the characteristics of the *pulsus celer*. It is, as a rule, of smaller volume, soft and often dicrotic. Like the other symptoms, this



pulse-rate varies with the exacerbations of the disease, with physical exertion, mental excitement, or again without any apparent reason at all. Its rhythm, as a rule, is dependent upon the cardiac rhythm, yet this is not always true, because if one auscultates the heart while taking the pulse, he may find an irregular pulse, while the heart action on the whole is regular though rapid. This only means that the cardiac muscle is incapable of transmitting each impulse to the periphery. Why? Is it purely on account of muscular weakness? Possibly so in some instances, but not always. This pulse arrhythmia may be due to extrasystoles, as is shown by electrocardiograms. According to Herring, these extrasystoles are caused by an irregular cardiomuscular impulse determined by some disturbances in the cardiac nervous system. There can be no doubt that in a great many instances the pulse irregularities are of nervous origin. In Basedow's patients these irregularities are so often dependent upon the nervous, psychic condition of the patient, and they follow so closely their fluctuations, that it is impossible not to recognize an etiological relation between them and these irregularities. This is so true that one can find great variations in the pulse-rate of a Basedow patient inside of a very few minutes. I have not infrequently seen a pulse-rate fall from 125 to 90 while taking the pulse and drawing the patient's attention to something else. In some patients the pulse-rate varies with each respiration. A nervous origin, however, cannot be ascribed to the *pulsus irregularis perpetuus*. It is of cardiac origin and caused by myocarditis.

At any rate, be it what it may, a constant cardiac arrhythmia is of bad prognosis; it shows that the strength of the heart is reduced, and since in Basedow's disease the heart is the organ mostly endangered, we must consider arrhythmia, when present, as a very important prognostic symptom; it shows that the cardiac mechanism is out of gear and nearing exhaustion. It does not necessarily follow that cardiac muscular weakness and insufficiency must always be accompanied by arrhythmia. One would indeed meet with disappointment if he should regard a heart as strong and safe because it beats regularly. Once in a great while, one will venture into a surgical operation and be absolutely deceived as to the real value of the cardiac muscle; the heart is regarded as capable of standing the surgical strain, and yet, when the time comes, there is not even a show of a fight; the heart simply quits. On the other hand, a slight degree of arrhythmia is not an absolute contraindication to operation. Nothing is, indeed, more difficult to judge than the strength of the heart. We must consequently grasp every information we can get in order to draw safe conclusions. Therefore we must consider cardiac arrhythmia, even slight, as a very good *warning symptom*: it would be unpardonable not to give it its due consideration.

**Test of Functional Capacity of the Heart.**—For several years I have used the *Katzenstein test*. This test is as follows: Both femoral arteries are firmly compressed with the fingers below Poupart's ligament until pulsations are suppressed. The blood-pressure and pulse-rate are recorded before, and again after pressure on the arteries has been applied for two or three minutes. With a sound heart the blood-pressure is found higher afterward and the pulse slower. If the blood-pressure and the pulse have not changed, this shows that the heart is not quite normal, but not actually incompetent. If blood-pressure remains the same, but the pulse increases, this shows a higher degree of insufficiency. If the blood-pressure is found lower and the pulse-rate higher, this warns us of severe functional cardiac disturbances. Their severity is in proportion to the extent of the drop in the blood-pressure and of the increase in the pulse-beat. When the test shows marked functional insufficiency, Katzenstein advises against any operation, unless the indications are vital, and then only under local anesthesia. I have found the Katzenstein test a valuable adjunct to the other clinical diagnostic means we possess.

*Blood-pressure* is, as a rule, of medium strength and varies between 100 and 150. A high blood-pressure is unusual.

## CHAPTER XXII.

### BASEDOW STRUMA.

THE enlargement of the thyroid gland in Basedow's disease is another of the most important cardinal symptoms; it is the one which in true exophthalmic goiter seldom fails. This is so true that Kocher has said, "No goiter, no Basedow's disease." Such a dogmatic statement suffers exceptions, however, since in certain cases even the most expert is unable clinically to determine with certainty whether there is an enlargement of the thyroid gland or not, yet at the operation, one is almost always astonished to find the gland larger than normally. As a general principle, it may be said that whenever the thyrotoxic clinical complex is present, there is always at some stage or another during the course of the disease hyperplasia of the thyroid. This hyperplasia may not be detectable clinically, but is present microscopically, as we shall see later on when studying the pathology of the thyrotoxic gland. In cases in which hyperplasia of the thyroid is apparently absent, if a careful retrospective history is taken, one will find, as a rule, that there has been thyroid enlargement at one time or another. It must not be forgotten that thyroid enlargement is liable to undergo great fluctuations, that it may be more marked at times than at others, that it may even show up only quite a long time after the other thyrotoxic symptoms have appeared. I can recall a few cases in which the thyroid enlargement became detectable clinically only months after the other symptoms of Graves's disease were well established.

At any rate one thing is certain: *the volume of the thyroid is not at all proportionate to the severity of the disease.* It is not the largest goiter that causes the most symptoms; sometimes most severe cases of Graves's disease are seen where very little or no apparent enlargement of the thyroid gland is present, whereas large goiters are often accompanied by little or no thyrotoxic symptoms.

Thyrotoxicosis may develop in patients whose thyroid gland has been previously normal, or in those previously affected with goiter, whatever it may be, colloid, cystic or malignant. In the first cases, the exophthalmic goiter is called *primary*: in the second case it is called *secondary* or *Basedowified goiter*.

The exact distinction between primary and secondary, or Basedowified goiter, is in certain cases difficult, and sometimes even impossible.

Of course, in a great many instances the distinction is easy. Take, for instance, a young, nervous woman who never had anything the matter with her neck, and who after emotion, worry, overwork, or some acute infection, develops a rapid heart action, palpitation, tremor, insomnia, exophthalmos with Graefe, Stellwag and Moebius symptoms, and who at the same time shows an enlargement of the thyroid with vascular symptoms developed in it. Here no one would hesitate; this is a *primary thyrotoxic goiter*, because the enlargement in this case has occurred in a gland which was previously absolutely normal. Take, on the other hand, another patient who has had for many years a cystic or colloid goiter which never caused very much trouble, except possibly some pressure symptoms. Suddenly or gradually, with or without any apparent cause, this patient becomes nervous, complains of palpitation, tremor, shows exophthalmos, and in short, exhibits a train of symptoms which are unmistakably thyrotoxic. This is a *secondary thyrotoxic goiter*, because previous to this condition the patient has had for years a harmless goiter. This simple goiter has become a *Basedowified one*. These distinctions, however, are not always so simple. There are cases, indeed, of secondary exophthalmic goiter in which the thyroid gland has become of such a thyrotoxic type, that unless the case has been seen previously, it is no longer possible to say offhand whether the case is primary or secondary. The physician will then have to rely entirely upon the history of the case.

One may think the distinction between these two forms of goiter devoid of interest. Therein lies a mistake, for the distinction between the primary and the secondary, or Basedowified goiter, is of great clinical and prognostic value. A Basedowified goiter will respond to surgical treatment far more readily and safely than a primary one.

The *volume* of the thyrotoxic goiter is exceedingly variable. In the primary form the hyperplasia is diffuse and involves both lobes, the isthmus, and the pyramidal process. It is true that one lobe may be affected more than the other. In that case the larger lobe will rarely exceed twice the size of a goose egg, and the right lobe will be more often involved than the left. In the secondary form, or Basedowified goiter, the goiter may have all kinds of dimensions: the volume in this form depends upon the size of the preëxisting, non-toxic goiter, whether it be colloid or cystic, and to it, of course, we must add the thyrotoxic hyperplasia and hypertrophy of the remaining normal parenchyma of the gland.

The *consistency* of the thyrotoxic goiter depends largely upon the variety of goiter with which we have to deal, and with the stage of the disease. In the early beginning of the primary form and sometimes in the regressing period of the disease the gland is mostly soft, but as



soon as thyrotoxicosis is well established the goiter becomes firm and elastic, while in advanced conditions it becomes of much harder consistency. In the last stage, where the gland has become exhausted and is undergoing a cirrhosis, it is truly hard. In the Basedowified goiter, of course, the consistency will depend upon the nature of the preëxisting goiter; the gland, however, will show more firmness to the touch than during the non-toxic period.

Pressure over the thyrotoxic goiter, especially in the early stage of its development, is painful; this is a very good diagnostic point.

The *surface* of the primary thyrotoxic goiter is finely granular. This sensation is given by the distended alveoli bulging under the capsule of the thyroid gland. In the secondary form the surface is nearly always nodular and depends upon the surface and form of the preëxisting goiter.

The true primary exophthalmic goiter very seldom causes marked *dyspneic symptoms*, since its size is not great enough to cause compression of the trachea. Pressure symptoms, however, may occur when the lobes extend posteriorly and inwardly so as to form a circular goiter around the trachea. In the great majority of cases the shortness of breath which is often complained of by Basedow patients is mostly of nervous and cardiac origin. In the Basedowified form of exophthalmic goiter, of course, the shortness of breath is more apt to be of mechanical origin, being caused by the size of the goiter itself. Vascular symptoms play their part, too, since they increase the size of the goiter and thus increase the pressure.

More than the normal thyroid, the thyrotoxic goiter is apt to be influenced by the various physiological processes of the organism, such as menstruation, pregnancy, etc. The goiter reacts then by a more or less marked temporary enlargement, which retrocedes as soon as the process is over. Hence the complaint is often heard that the neck gets larger at each menstruation, pregnancy, etc. Psychic disturbances such as anger, fright, etc., have the same effect. At such times the vascular symptoms of the thyroid may become so marked that the subjective symptoms, such as shortness of breath, sensation of constriction in the neck, etc., are more evident.

**Vascular Symptoms of the Thyroid.**—The exophthalmic form of goiter is above all a *vascular* goiter. This feature has been observed by everyone who has had experience with Graves's disease. Vascular symptoms are of great diagnostic value. They consist chiefly of:

1. *Pulsation of the thyroid.*
2. *Thrill.*
3. *Murmurs.*

These symptoms may be seen, of course, in the non-toxic vascular

goiter, but the latter type will not be mistaken for a thyrotoxic goiter, since no symptoms of thyrotoxicosis will accompany it. If they do, it is no longer a simple vascular goiter but a thyrotoxic vascular goiter. It goes without saying that the simple vascular goiter may become thyrotoxic, as shown by A. Kocher. In the few really vascular goiters which I have seen, the vascular symptoms were all that I could detect. The patients had none of the thyrotoxic symptoms found in Graves's disease. Vascular symptoms may be found, too, in simple goiter. Here, however, an examination made with care will reveal that this simple goiter is undergoing thyrotoxic changes. In other words, it is becoming a secondary exophthalmic or Basedowified goiter. The vascular symptoms, consequently, retain a great diagnostic significance. They are, of course, not always present, and when present, may vary in intensity.

Simple inspection will reveal an intense *pulsation* of the entire gland and of the whole cervical region; the carotids beat violently and the thyroid is the site of a marked pulsation. In severe cases it is not infrequent actually to see the enlarged and tortuous branches of the superior thyroid artery beating under the skin. The gland in certain cases can be compared to a vascular sponge which can be squeezed at will, and by so doing, reduced considerably in size.

The vascular thyrotoxic goiter expands like an aneurysm. This *expansile pulsation* must not be mistaken for the *transmitted one*. Indeed, sometimes one may think that he has to deal with an expansile pulsation when the gland is only displaced *en masse*, forward and backward, by the violent carotid beats. The pulsation of the thyroid gland is then only a transmitted one. The best way to determine whether pulsation is expansile or transmitted is to grasp the whole gland in the palm of the hand and to exert a moderate compression. The gland will then be felt expanding as in an aneurysm. If no expansion is felt the pulsation is then a transmitted one.

Very often, especially in thin patients, a *venous pulse* is present; it is soft and is not synchronous with the cardiac pulse. It occurs mostly in the median and jugular veins. This venous pulse is nearly always negative. In rare cases, however, it may be positive and is then directly transmitted from the heart on account of the insufficiency of the tricuspid valve. It has been said that a positive venous pulse may be caused by a direct transmission of the arterial beat through the thin walls of the venous trunks.

Palpation with the thumb over the thyroid gland, and especially over its vascular poles, will reveal the presence of a *thrill*, while auscultation over the same regions will reveal the presence of *murmurs*. These murmurs vary in intensity and are more or less musical in character, and, as a rule, systolic; rarely, are they continuous, and when they are so they

show an exacerbation of tone during the systole. These murmurs may be heard all over the gland but acquire their maximum of intensity at the vascular poles of the thyroid, especially the superior ones, while often they are heard only there. If they are not so easily heard over the inferior thyroids, it is because these vessels lie deep, whereas the superior ones are more superficial. If an ima artery is present, the systolic murmur will be heard over it also. These murmurs may be heard over the large veins in the supraclavicular regions; they are then continuous and resemble the "bruit-de-none."

The latter ones are, as a rule, not of thyrotoxic origin.

The significance of these thrills and murmurs is not entirely understood. In ordinary cases of arterio-venous aneurysm the thrills and murmurs are caused by the passage of a column of blood through a constricted canal or opening leading into wider cavities where pressure is lower. In false aneurysms the thrill and murmurs are due solely to the passage of the volume of blood through a spasmodically constricted segment of an artery into a larger segment of a vein. There is abnormal communication of the artery with the veins. In thyrotoxic goiters we most likely have to deal with the same underlying principle.

The bloodvessels in thyrotoxic goiter are exceedingly thin and friable. This condition will explain, partly at least, why operations for exophthalmic goiter are usually more bloody than operations for simple goiter. This, however, is not the only reason, because we shall see that the blood of Basedow patients contains an increased amount of anti-thrombin, and for this reason its coagulability is diminished.

## PATHOLOGY AND HISTOLOGY OF THYROTOXIC GOITER.

Although Lubarsch and Marchand, in 1896, and Askanazy, in 1898, recognized some of the microscopical peculiarities of thyrotoxic goiter, it is really to A. Kocher and to L. B. Wilson that we owe our knowledge, not only of the pathological changes in the thyroid, but also of their real significance. They have brought this question to its real focus; and it is they who have established the true relation between the clinical symptoms and the pathological findings.

The thyrotoxic gland when seen *in situ*, as during operation, is often surrounded by a layer, more or less thick, of loose connective tissue, which renders it adherent to the neighboring tissues, especially the wind-pipe and the carotid sheath. The condition resembles the one seen after treatment with the x-rays, or the one which follows a mild degree of thyroiditis. This production of the connective tissue is most likely due to a chronic irritation caused by the thyrotoxin, and has been regarded by some as proof in favor of the infectious origin of Graves's disease.

On the cut surface the primary, thyrotoxic goiter is dry, gray or yellowish gray, and exudes very little or no secretion at all. The most

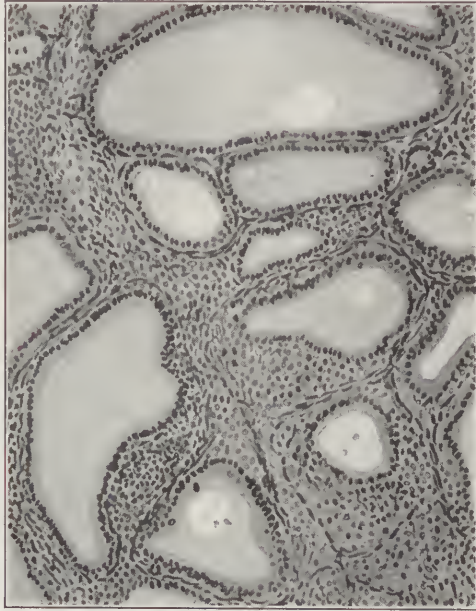


FIG. 68.—First stage of thyrotoxic cellular hyperplasia.  $\times 160$ .

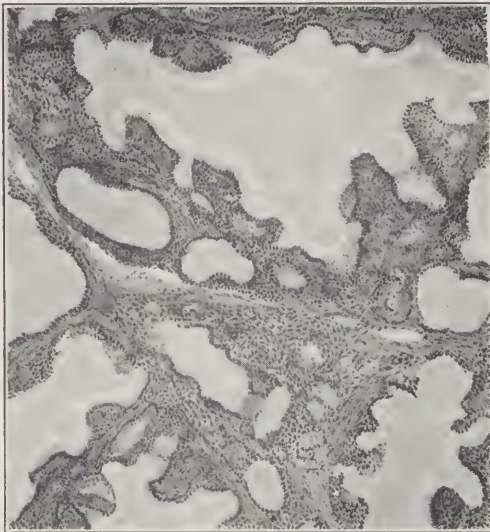


FIG. 69.—Advanced stage of thyrotoxic cellular hyperplasia.  $\times 80$ .

interesting features, however, are the microscopical ones. These peculiarities may be summarized in the following manner:



1. The alveoli are increased in size and number, and this increase is in proportion to the severity of the disease. They have lost their round

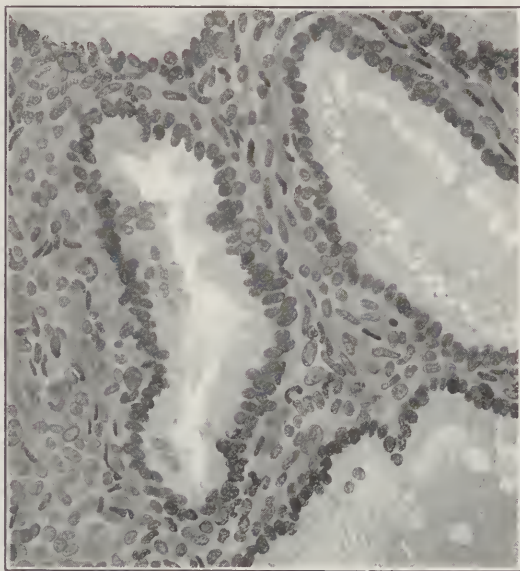


FIG. 70.—Advanced stage of thyrotoxic cellular hyperplasia. Note reduplication of alveolar cells.  $\times 360$ .

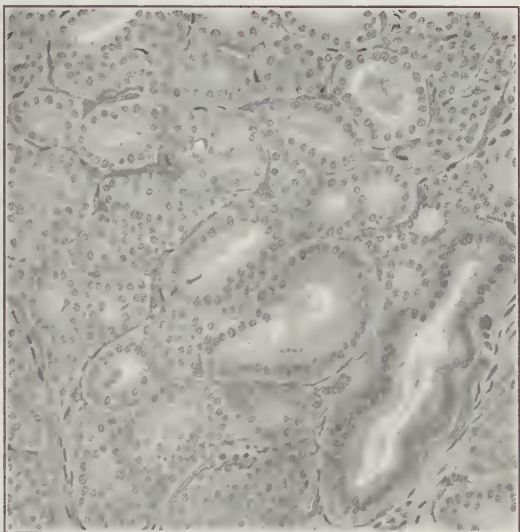


FIG. 71.—Last stage of thyrotoxic cellular hyperplasia. Note the alveolar lumina have almost entirely disappeared and are filled with cells.  $\times 200$ .

or oval shape and have become irregular and polyform (Fig. 68). This irregularity is intended to increase the lining capacity of the alveoli in order to accommodate the increased number of epithelial cells.

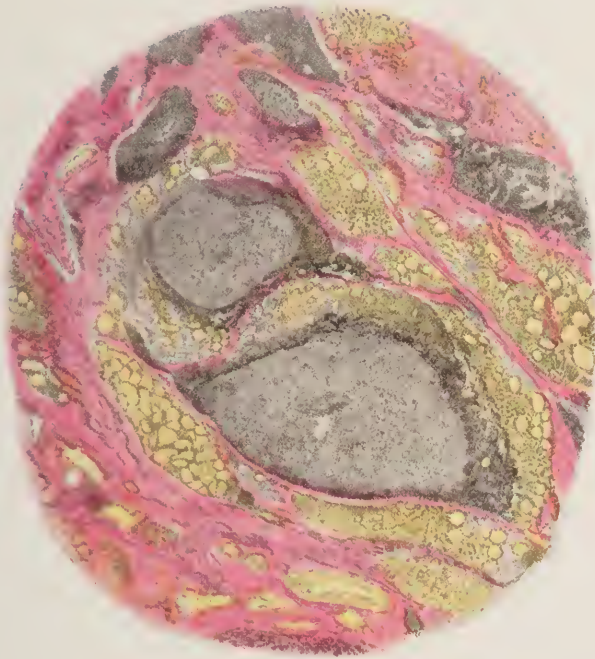
2. In normal alveoli the epithelium lining their walls is low cuboidal. In thyrotoxic conditions the epithelium becomes cubic, highly cylindrical (Fig. 69), affects the columnar type, and increases not only in size but also in number. Sometimes cellular hypertrophy and hyperplasia are so marked that the epithelium can no longer line the walls of the alveoli in one continuous layer, but is then forced to bulge out and give rise to papillary formations in order to make room for every cellular element. Even this may not be sufficient, since proliferation may be so marked that the epithelium has to dispose itself in two or three layers, one lying on top of the other; sometimes the alveoli are entirely filled with epithelium only. In some instances proliferation may be so intense that the epithelial cells do not even attempt to shape themselves into alveoli; they lie without order, thus giving rise to microscopical pictures very similar to those of malignant adenoma. The protoplasma of the thyrotoxic cells is clearer than the normal ones; their nuclei are basal, and, as a rule, are not very much larger than the normal. As shown by McCallum, mitosis is quite frequent, a sign which must mean an increased glandular activity. Very often a number of desquamated cells undergoing cytolysis are found floating loosely in the lumen of the alveoli. This desquamation and cytolysis are always of ill omen, so far as prognosis is concerned.

3. In normal thyroids as well as in simple goiters the colloid is thick and stains readily. In thyrotoxic goiters the colloid is thin and takes the stain with difficulty or not at all. Ischenschmid has shown that this fluid colloid takes the stain differently from the normal colloid. It becomes eosin-red with the hemalaun-eosin stain, whereas the thick colloid found in simple goiters or normal thyroids becomes blue or red. This may be regarded as a good proof that this colloid is chemically different from the normal one. It thus becomes easy to understand, too, that colloid in thyrotoxic goiters, being far more fluid and thinner than the normal, will be that much more readily absorbable.

4. In simple colloid goiters small foci of leukocytes are sometimes found here and there throughout the stroma of the gland; in normal thyroids nothing of the kind is seen. In Graves's disease, on the contrary, they are very frequent and numerous; these leukocytic foci recall the formation of a lymph node. Not infrequently they have a clear, plain germinal center. (Plate X.) The significance of these leukocytes is not clear. They are considered by some as belonging to the status lymphaticus, and by some others as a proof of a chronic irritation by the thyrotoxin, and would be, in other words, the equivalent of a chronic thyroiditis.

Now comes the important question: Are the microscopical changes found in thyrotoxic goiter constant and specific of the disease? I do

PLATE X



Leukocytic Infiltration with Germinal Centers in a Thyrotoxic  
Parenchymatous Goiter.  $\times 46$ .





not think that I could do better than to quote verbatim L. B. Wilson: "By assuming that the symptoms of true exophthalmic goiter are the results of an excretion from the thyroid, and by attempting to determine the amount of such excretion from pathological data one is able to estimate in a large series of cases the clinical changes of the disease with about 80 per cent of accuracy, and the clinical severity of the disease with about 75 per cent of accuracy. It would therefore appear that the relationship of primary hypertrophy and hyperplasia of the parenchyma of the thyroid to true exophthalmic goiter is as direct and as constant as a primary inflammation of the kidney to the symptoms of Bright's disease. Any considerable findings to the contrary I believe to indicate either inaccurate or incomplete observations on the part of the pathologist or clinician, or both."

I can but subscribe to this statement. In the great majority of my cases I was able to determine quite accurately the severity of the disease by simply looking at the slides, being careful not to know beforehand from what patient they came. In a certain number of cases I was surprised not to find the characteristic changes, or not to find them in proportion to the severity of the disease. If new sections, however, were made of different portions of the excised gland, then the characteristic pathological changes could be found in places, thus supporting fully Kocher's statement that thyrotoxic hyperplasia may be localized to circumscribed areas. These Basedow islands may be either the beginning of microscopical changes which are going to involve the whole gland, or they may be the remainder of a regressive process which is going to transform the thyrotoxic goiter into a colloid goiter. We must always bear in mind that in the natural course of things, if the patient lives long enough the thyrotoxic goiter is destined to become a colloid one. Inasmuch as during the thyrotoxic stage, the gland is burning itself up, if the process lasts long enough, exhaustion is bound to come. The gland enters the regressive period; connective tissue gradually invades and takes the place of the noble elements, and what remains of the alveoli becomes colloid in type. These two processes, namely, colloid regression and cirrhosis of the gland, are bound to depreciate and diminish the secreting power of the gland, hence hypothyroidism; hence myxedema. We may, consequently, say that a Basedow patient, if he is not killed meanwhile by his thyrotoxicosis is logically destined to become myxedematous, provided, of course, the toxic process lasts long enough.

In the secondary or Basedowified goiter the same pathological findings characteristic of Graves's disease will be found. They will be most developed at the periphery of the gland and at the vascular poles.

It is true that sometimes in young individuals, and especially at the

time of puberty, hyperplastic islands similar to those seen in thyrotoxicosis will be found spread throughout the normal parenchyma. They may, of course, have a thyrotoxic signification; it is not, however, always necessarily so, because they may be interpreted as some non-toxic compensatory proliferation of the thyroid.

### MITOCHONDRIA.

Struck by the fact that cases with thyrotoxic symptoms had been relieved from such symptoms by removal of the apparently simple adenoma, and that the microscopical examination of the tumor did not show any of the usual signs of functional cellular hyperactivity, such as increased size of the cells, diminution of the colloid, increased vascularity, etc., Goetsch sought to determine whether in such cases signs of functional cellular hyperactivity were nevertheless present. He applied the *Bensley technic* for the study of mitochondria.

This technic is as follows: The tissues to be examined must be absolutely fresh and must be placed in a fixation fluid in small pieces immediately after removal from the body. The fixation fluid is an osmic acid, bichromate of potash, and acetic acid mixture, and the subsequent staining consists in the application, after mordanting with potassium permanganate, of acid-fuchsin with a counter-stain of methyl green. The mitochondria are stained a brilliant red and are readily recognized.

With such method Goetsch was able to show that there was a very marked increase in the number of mitochondria in the apparently torpid adenomata of the thyroid, thus showing that although ordinary signs of thyroid hyperactivity are absent, one has the right to assume that cellular functional hyperactivity is nevertheless present, since mitochondria are regarded by all authorities as a sign of cellular functional hyperactivity.

Mitochondria were first observed by Altmann in 1890, and were called by Romeis, *plasmosomes*. Mitochondria are structures occurring in the cytoplasm of all cells. They occur in the form of granules, rods or filaments. Observed in living cells they show frequent changes in their form. In their solubility and staining reactions they resemble phospholipins, and to a lesser extent, albumins. They are present in the cells of animals as well as in those of plants and are more abundant in the active stages of life of the cells, and diminish progressively in number as the cells become senile. They are particularly abundant in immature embryonic cells in which metabolism is very active. All these facts and many others seem to confirm the opinion of investigators that mitochondria take an active part in metabolism.

If we study the mitochondria picture of the normal thyroid and of the

toxic adenoma, we shall find that in the former the number of mitochondria is exceedingly reduced and that there is no intrafollicular colloid present, while in the second case the number of mitochondria is exceedingly increased and the intrafollicular colloid is very abundant, consequently the claims made by Goetsch that the study of mitochondria, or rather that the mitochondria will prove to be a better index of thyroid activity than the histological criteria heretofore applied, are well grounded.

### ADENOMA WITH HYPERTHYROIDISM AND EXOPHTHALMIC GOITER.

Recently, Plummer has sought to establish a fundamental clinical difference between exophthalmic goiter and adenoma with hyperthyroidism. (Exophthalmic goiter corresponds to what I call *Primary Thyrotoxic Goiter*, and Adenoma with Hyperthyroidism to what I call *Secondary Thyrotoxic Goiter*.) In Plummer's judgment, the differences between these two conditions are so striking that one is warranted in considering them as two distinct clinical entities. The most essential difference between the two conditions, in Plummer's judgment, is the absence of exophthalmos, or practically so, in all cases of adenoma with hyperthyroidism, while it is almost always present in exophthalmic goiter. To quote Boothby, who accepts unqualifiedly Plummer's views: "Exophthalmic goiter has a different clinical course from adenoma with hyperthyroidism, and, in addition, certain peculiar and characteristic symptoms, one or more of which are present in varying degrees, such as exophthalmos, thrill and bruit, tendency to gastro-intestinal crises, and a peculiar type of nervousness. That we are dealing with two entirely distinct diseases in exophthalmic goiter and adenoma with hyperthyroidism has been proved beyond reasonable doubt by Plummer by the difference in the mode of onset of the two diseases, the clinical course and duration of symptoms, physical findings, and finally the difference in the pathology of the gland."

So far as I am personally concerned I am unable to accept the duality of thyrotoxicosis.

In my judgment, this disease still retains its fundamental unity, and the differences observed are solely differences of degree of intensity. In the primary thyrotoxic goiter, or the "exophthalmic goiter" of Plummer, the gland shows its maximum of functional activity, hence the intensified symptomatology, while in the secondary thyrotoxic goiter, or the "adenoma with hyperthyroidism" of Plummer, the gland is, as a rule, much less active. This view is strengthened by the basal metabolism, by the blood supply of the gland, and by the pathological examination

of the gland. In that we concur with Boothby when he says, "Pathological variations in the basal metabolic rate are due to either increase or decrease in the thyroxin volume, thus explaining the characteristic or fundamental alterations in the basal metabolism found in hyperthyroidism and in hypothyroidism."

In non-toxic conditions, the diffuse colloid and adenomatous goiter, everything being equal, must be considered as possessing a lesser physiological activity than the normal thyroid. This being the case, a normal thyroid undergoing an acute hyperfunction will translate its effects in a far more marked manner than the diffuse and adenomatous goiter. This is the reason why a primary thyrotoxic goiter, or the "exophthalmic goiter" of Plummer, shows a far more active symptomatology than does a secondary thyrotoxic goiter, or the "adenoma with hyperthyroidism" of Plummer. If one wishes to be convinced of this fact, let him compare the clinical picture observed in acute primary toxic goiter, or the "exophthalmic goiter" of Plummer and that of a severe secondary toxic goiter, or the "adenoma with hyperthyroidism" of Plummer. No fundamental clinical difference will be observed, except only a difference of intensity.

So far as exophthalmos is concerned, anyone, I am sure, has observed severe cases of primary thyrotoxic goiter, or the "exophthalmic goiter" of Plummer, without any ocular symptoms whatsoever, such as exophthalmos, Graefe, Moebius, Dallrymple, Kocher, Stellwag, etc. On the other hand, in secondary thyrotoxic goiter, or "adenoma with hyperthyroidism" of Plummer, more than once the ocular symptoms have been very marked, exophthalmos included. That they are, however, more frequent and, in a general way, more intensified, in the primary than in the secondary thyrotoxic goiter, I am willing to admit. But this is again only a matter of degree.

So far as the other symptoms are concerned, such as vascular symptoms in the thyroid, tendency to gastro-intestinal disturbances, nervousness, etc., although again usually not so intense or so frequent as in the primary form of thyrotoxicosis, or the "exophthalmic goiter" of Plummer, they are so frequently enough present to preclude a fundamental clinical difference between the two conditions, namely, the primary form of thyrotoxicosis, or the "exophthalmic goiter" of Plummer, and the secondary form of thyrotoxicosis, or the "adenoma with hyperthyroidism" of Plummer.

The surgical results obtained speak also against a fundamental clinical difference of these two conditions. They rather corroborate the opinion that these two conditions are purely a matter of degree because the secondary form of thyrotoxicosis, or the "adenoma with hyperthyroidism" of Plummer, responds far more readily to surgical interference than does the primary form, or the "exophthalmic goiter" of



Plummer. The beneficial results obtained in the first condition are far more rapid and complete than in the second case because of the difference in the functional activity of the gland.

The age of incidence in these two conditions has no fundamental bearing, but rather supports again the view that we have to deal with a difference in degree in the same condition. The secondary form of thyrotoxicosis occurs late in life because the diffuse and colloid adenoma reaches its maximum in middle age.

Thus, in my judgment, the positing of a fundamental clinical difference between these two conditions is unwarranted.

## CHAPTER XXIII.

### OCULAR SYMPTOMS.

THE ocular symptoms, especially exophthalmos, have always been among the most striking features of Graves's disease; they are the symptoms which from the earliest times have struck the attention not only of the medical profession, but also of the laity. They are the features, too, from which the disease has taken its distinguishing names: as, for example, *exophthalmic goiter*, *Glotzaugenkrankheit*, *Morbo esotalmico*, etc., just as if the ocular pathology alone seemed to constitute the whole disease. By ocular symptoms we refer to a group of symptoms, some involving the globus oculi itself, some others the eyelids, and again others taking their origin in a distorted coördination of the orbital musculature. These symptoms are *exophthalmos* and the *Dallrymple*, *Graefe*, *Stellwag*, *Kocher* and *Moebius* symptoms.

**Exophthalmos.**—Exophthalmos, though one of the cardinal symptoms of Graves's disease, yet is not so constant as some of the other clinical symptoms. Usually it appears when once the disease is already established; exceptionally, however, it may appear at the onset of the disease as the first manifestation. Sometimes it never shows up at all. Unlike the other symptoms seen in thyrotoxicosis, exophthalmos is very much less subject to fluctuations. Even when all the other thyrotoxic symptoms undergo material improvement, exophthalmos may show little or no change. It is the most stubborn and the most discouraging of all the features of Graves's disease. Even years after everything else has almost entirely subsided, exophthalmos still remains as the living witness of the past thyroid pathology.

Exophthalmos is best seen in profile, although in ordinary cases the front view will reveal the conditions just as well. It takes place directly forward, following the axis of the orbita. Exophthalmos, as a rule, affects both eyes. It may be more marked in one eye than in the other and in the rarer cases it may be purely and primarily *unilateral* (Fig. 72).

**Unilateral Exophthalmos**, however, is not such a rarity after all. Sattler was able to find 109 cases in the literature. In 46 cases the exophthalmos was on the right side; in 40 cases it was on the left, while in the remaining 23 cases the side was not given. Furthermore, Sattler found that in 43 cases of unilateral exophthalmos, 17 times the exophthalmos was on the same side on which the thyroid hyperplasia was

most developed, 14 times on the right side, and 3 times on the left side, while in 6 cases the unilateral exophthalmos was developed on the opposite side to the one on which the thyroid development was most marked.

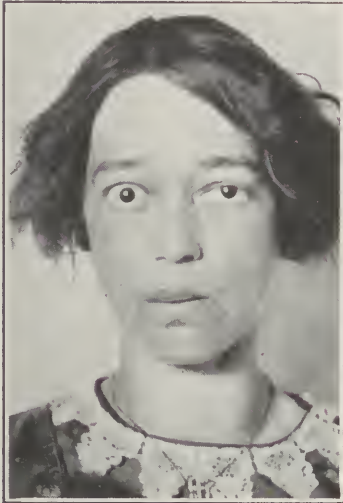


FIG. 72.—Unilateral exophthalmos.



FIG. 73.—Bilateral exophthalmos.

**Bilateral Exophthalmos.**—A bilateral exophthalmos may become unilateral in the course of the disease, and this is especially true when an operation on the thyroid, such as a ligation or a unilateral lobectomy, has been performed. When that is the case, exophthalmos, as a rule, disappears on the side corresponding to the one which has been operated on. However, this retrocession of exophthalmos is, as a rule, only temporary; the exophthalmos returns to its previous intensity.

The degree of exophthalmos is extremely variable and may fluctuate, although in less degree than the other thyrotoxic symptoms, with the period of the disease, with the physical and mental condition of the patient, or with no apparent reason whatsoever. It becomes most intensive during periods of exacerbation of the disease and during excitement (Fig. 73). The degree of exophthalmos is not, as a rule, in proportion to the severity of the disease, since it may be extremely marked in light cases of thyrotoxicosis, and scarcely apparent in severe cases of Graves's disease. In some cases the protrusion of the eyes is so marked that the patient can no longer bring the upper eyelid into contact with the lower. They remain apart so that a portion of the eyeball is seen through the half-closed lids, and this is especially true during sleep, because at that time no voluntary effort intervenes. Some authors, as

Trousseau, Zimmerman, Rehn and Tucker, have reported cases of complete dislocation of the eyeball, and Deschamps and Perriol have described a case in which the eyeball had completely bulged out of the orbital cavity, and in which necrosis of the cornea had followed.

Frank H. Lahey, in 1920, reported the case of a woman, admitted to the ophthalmological service of the Boston City Hospital, with a past history of admission as an out-patient at another hospital a year previously, where she had been treated for hyperthyroidism by means of  $x$ -rays. Following this treatment her pulse had come down; she had gained in weight, and her general condition had improved, but the exophthalmos had continued to progress until edema and ulceration of her right cornea were such that she came to the Boston City Hospital, where enucleation of the right eye was done. He was asked to see her a month later on account of the increasing exophthalmos and edema of the left eye, and it was decided to attempt by surgical measures to preserve this remaining eye. Because of the belief that recession of the protruding eye occurs after removal of the sympathetic ganglion on the affected side, the operation for the removal of the superior cervical sympathetic was carried out, and at the same time the external canthus was incised to relieve the pressure of the lid edges. Progress of the edema continued in spite of these procedures, whereupon two days later the lids were sutured together, but still edema and ulceration continued until enucleation of the remaining eye became necessary.

Not infrequently, the degree of exophthalmos is so slight that it is difficult to decide whether it is pathological or not. This is not uncommon with large, protruding eyes, yet such people may not have the slightest sign of Graves's disease. It is that much more difficult to decide whether the apparent protrusion is pathological or not, since the relations between the globus oculi and orbita vary greatly, not only with each individual, but also in the same patient when both sides are compared. It is only after comparing photographs of the patient taken before and after his thyrotoxic condition, and by taking into consideration the statements of the immediate members of his family, that judgment can be passed.

A. Kocher and Sattler undertook to establish what were the normal relations of the eyeball to the orbita, using for that study the exophthalmometer of Birch-Hirschfeld. They found that in many cases the globus oculi would protrude more than normally, yet no one could say that exophthalmos was present. As soon, however, as there was at the same time an enlargement of the palpebral fissure, then only did exophthalmos become apparent.

In some cases auscultation over the protruding eyes has betrayed the presence of murmurs, which have been interpreted by several authors



as being of vascular origin. E. Herring demonstrated, however, that these murmurs heard over the eyeball were of muscular origin. They are heard only when the eyelids are shut, increase in proportion to the intensity of the occlusion of the eyelids, and disappear as soon as the muscular contraction ceases. These murmurs resemble the placental murmurs heard in pregnant women; they are also found in normal individuals. They seem to have sometimes a decided systolic character, and may then be partly in relation to the increased vascularization of the orbita.

Usually the ocular movements in Basedow patients are not materially hampered; it is, however, not so rare to find a diminution of the upward and downward amplitude of movement. This is very likely due to the fact that the eyeball, being pushed forward, has its center of rotation displaced; hence the disturbance in the ocular mechanism. Curiously enough, even marked exophthalmos causes little or no discomfort to patients. All that they may complain of is the sensation of a forward pushing of both eyes.

**Eyelid Symptoms.**—Under this name we understand several symptoms peculiar to Graves's disease, yet not pathognomonic and not always constant. These are the Dallrymple, Graefe, Kocher and Stellwag symptoms.

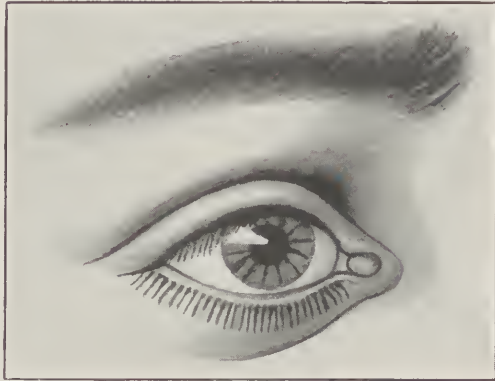


FIG. 74.—Normal eye.

**Dallrymple Symptom.**—In order to be normal, the palpebral fissure must meet certain requirements (Fig. 74). In normal conditions the superior eyelid covers a small portion of the cornea, whereas the lower eyelid reaches the edge of the cornea. In Graves's disease the angle of aperture is greatly increased; both eyelids are farther apart, leaving uncovered not only the cornea, but also a greater or smaller portion of the sclerotica. This abnormal enlargement of the palpebral fissure is called the Dallrymple symptom. This finding is entirely independent of the

exophthalmos itself, since it is often present, as shown by the exophthalmometer, when little or no protrusion of the eyes can be found. *Vice versa*, we may have a very marked exophthalmos with a normal, or only moderate, enlargement of the palpebral fissure. In the majority of cases, however, it is this pathologically enlarged palpebral fissure which creates the impression that we have to deal with a marked protrusion of the eyes.

Enlargement of the palpebral fissure does not necessarily mean that we have to deal with a thyrotoxic condition, since it is often found in normal individuals. We know that normally some people have very large, prominent eyes and that some others have very small ones. This fact depends greatly upon the degree of enlargement of the palpebral fissure.

**Graefe Symptom.**—The head being kept immobile, and looking forward and slightly upward, the patient is asked to fix his eyes upon an object, such as the finger of the examiner or a pencil moving slowly *downward*. Under normal conditions the upper lid follows the downward rotation of the globus oculi until the movement is terminated. There is, consequently, coördination between these two movements, namely, between the downward rotation of the eyeball and the downward following of the upper eyelid. In Graves's disease, however, the upper eyelid indeed begins the downward movement but does not finish it; it stops while the eyeball still continues to rotate downward. This is the Graefe symptom. It is due to a spastic retraction of the upper eyelid. In certain cases not only does the upper eyelid stop, but it even retracts suddenly upward. When the downward rotation is completed, if the eyeball is kept in that position for a time, the upper eyelid may then, too, follow and complete its downward excursion. If, however, the upper eyelid should not take its full downward course and remain retracted at a certain height, then when the globus oculi begins to rotate upward, the eyeball moves alone for a time, and only after a while does the eyelid start its upward movement. The Graefe symptom is not dependent upon the degree of exophthalmos itself, since it is found in cases where no, or little, exophthalmos is present. As with the Dallrymple sign, so the Graefe symptom is sometimes the earliest indication of the disease. It may be present or more developed on one side than on the other. In some individuals it may be present, or disappear under certain given conditions. For instance, Kocher was able to detect it only when the patient was in the lying position. It may be present at times and not at others, hence the necessity of numerous attempts at searching for this symptom.

The sign of Graefe when accompanied with some other thyrotoxic symptoms becomes of great diagnostic value; it may even be considered

as pathognomonic. It must be remembered, however, that in certain normal individuals the Graefe symptom may be positive. It has been found, too, in certain diseases of the nervous system such as hysteria, neurasthenia, epilepsy, myasthenia, paralysis agitans and bulbar paralysis of the eyes. In these cases we shall scarcely mistake one condition for the other; consequently the Graefe symptom in Basedow's disease retains its full diagnostic value.

**Kocher Symptom.**—While the point of a pencil, or a finger is held in front of the patient, on a horizontal plane with the line of vision, and the head is kept immobile, the patient is asked to follow with his eyes this pencil or finger point in its very sudden and abrupt *upward* movement. In normal individuals the upper eyelid will follow synchronously the upward rolling of the globus oculi. In Basedow's patients this may not be so. The upper lid may contract itself and rise slightly before the globus oculi has started its upward movement. The incoördination of these two movements is called the Kocher symptom. It may be considered as a modification of the Graefe symptom, but may be present when the latter is totally absent. Its etiological and pathological significance is the same as that of the Dallrymple and Graefe symptoms.

**Stellwag Symptom.**—In normal individuals the winking of the eyelids occurs from three to ten times a minute. In Basedow patients the number of these winks is markedly diminished. Sometimes there is scarcely one wink taking place during a whole minute, while even two or three minutes may elapse before any sign of winking is observed. This fact, known as the Stellwag symptom, was first described by C. H. Stellwag in 1869. It is quite frequent and was considered by Stellwag as of great diagnostic importance. But its diagnostic value has certainly been exaggerated because sometimes, and even in the most severe cases of Basedow's disease, it fails to be present. Indeed, in some cases the winking of the eyelids instead of being diminished, is increased in number.

**Moebius Symptom.**—In Basedow's disease the insufficiency of the converging power of the eye may be quite marked. The attention was called to this symptom by Moebius, hence the name. It was, however, also observed by Trousseau in 1862. The Moebius symptom is observed in the following manner: an object such as a finger or a pencil is placed at a certain distance before the patient, horizontally with the line of vision, and between the eyes. The patient is then asked to concentrate his look upon that object while it is brought nearer and nearer until convergence is necessary to see it still with both eyes. In normal individuals convergence may attain a marked degree before complaint is made, whereas in Graves's disease the convergence cannot be kept up. As soon as it has reached a certain degree, which varies with each indi-

vidual, convergence ceases; one of the eyes diverges, taking at once the previous position parallel to the line of vision, while the other eye still continues to converge and look at the object. This divergence constitutes the Moebius symptom. The insufficiency of convergence is not at all in proportion to the degree of exophthalmos, since it may be extremely marked in cases where the protrusion of the eyes is only moderate. It will be easily understood, however, that a marked exophthalmos can but increase the difficulty of converging. According to Sattler, when all sources of error have been eliminated, the Moebius symptom in Graves's disease is not so frequent after all. It should be considered as of thyrotoxic origin only when the refraction of both eyes has been controlled, skiagraphically or functionally.

The Moebius symptom is explained in the following manner by Landström: when the rectus internus muscle contracts itself, it rotates the globus oculi inward, thus putting the outer portion of the Landström muscle on the stretch. Since this muscle in Basedow's disease is permanently and pathologically contracted, it hinders the action of the rectus internus, and renders the convergence painful, hence causing the divergence of one of the eyes.

The *pupils*, as a rule, are not affected in Graves's disease. Numerous statistics show that in a very small percentage of thyrotoxic cases, they may be either dilated, contracted or unequal. None of these troubles, however, seems to be dependent upon the Basedow condition.

The *power of accommodation* of the eye is not disturbed either, for even in marked exophthalmos the power of vision is not altered. Intra-ocular alterations such as papillitis, optic neuritis, and optic nerve atrophy have rarely been seen.

*Nystagmus* is seldom found in Basedow.

**Lacrymal Secretion.**—There is sometimes an exaggerated production of tears which occurs without the presence of conjunctivitis, inflammation of the lacrymal ducts, or any other cause whatsoever. This exaggerated secretion of tears occurs by spells, and often during the night. Sometimes in advanced cases of Graves's disease there is a hyposecretion. These disturbances are very likely due to a neurosis of the secretory apparatus of the lacrymal ducts. They might possibly be due, too, to some alterations of the lacrymal glands themselves.

On account of the diminution of the sensibility of the cornea and conjunctiva, and on account of the protrusion of the eyeballs, and because of their diminished protection caused by the eyelid symptoms, and furthermore on account of the infrequency of the winkings of the eyelids, the eyes remain exposed more than normally to numerous injuries which in some conditions may lead to very severe ocular complications and inflammations such as conjunctivitis and keratitis.



When they occur these complications are peculiarly stubborn to treatment, and the reason may possibly be because they are partly due to some trophoneurosis.

**Staring Look.**—Now that we have studied all the ocular and eyelid symptoms, we shall be better able to understand the peculiar *staring* and *glaring look* which is so characteristic of Graves's disease, and which possibly more than any other symptom, has always impressed the laity. The eyes in Graves's disease have a look of fixity, of great surprise and sometimes of wild anger or terror, which has been called the "tragic stare" (Fig. 73). At the same time the eyes have always a peculiar brilliancy, a fact which has been observed since antiquity. The Germans call it the "Glanzaugen." A number of conditions concur to give birth to this staring and glaring look. The enlarged palpebral fissure, the exophthalmos, and the diminished winking of the eyes are the most important intervening factors. Under such conditions not only do the eyes protrude, but also a portion, more or less great, of the sclerotica is exposed, thus leaving a white, unprotected surface. Add to this the fact that, on account of the Dallrymple symptom, the eyes are less shadowed by the eyelashes; that, on account of the Stellwag symptom, the white sclerotica and the shining cornea form a glaring surface which is seldom interrupted by the winking of the eyelids, and finally, that the increased lacrymal secretion cannot but add materially to the brilliancy of the eyes by increasing the moisture all over their surface, then all these various factors will make us understand the pathogenesis of the staring look.

**Edema and Pigmentation of the Eyelids.**—Once in a while, true edema of the eyelids is observed. In some instances, however, this swelling of the eyelids does not pit on pressure, and is due, according to Eppinger and Sattler, to a deposit of fat, as is shown by postmortems. It is strange, indeed, to see fatty tissue deposited there when it has disappeared from all other regions of the body. Not so rarely, the eyelids are highly pigmented, thus forming a large, brown-black circle around the eyes. In severe cases this pigmentation is very marked and may coincide with pigmentation of other organs of the body. It is one of the cutaneous manifestations in Basedow's disease, and is probably of suprarenal body origin.

**Etiology of Exophthalmos.**—The pathogenesis of exophthalmos is a subject which has proved of great interest, and at the same time, a great puzzle to the scientists, who from the earliest beginnings of the knowledge of Graves's disease have tried to explain its etiology. In trying to explain the cause of exophthalmos one should not forget the following facts, namely: That if exophthalmos, as a rule, develops slowly and gradually, it may nevertheless develop rapidly; it is furthermore sub-

ject to fluctuations varying with the physical and mental condition of the patient and it may subside entirely after operations, or on the same day of the operation, to reappear again a few days after. All this is said to emphasize the *liability of exophthalmos to rapid changes*. This fact being first agreed upon, then at once a number of theories which have been advanced in explanation of the etiology of exophthalmos must be discarded. *Ipsa facto* this is true of the theory which was upheld by Jeandrassik and Mendel, namely, that exophthalmos is caused by abnormal deposit of retrobulbar fat. The same is true for Cooper's and Egberg's theory, which claimed that exophthalmos is due



FIG. 75.—Sagittal cut through eyelid and eye: 1, tarsal cartilage; 2, Müller's muscle; 3, eyelid; 4, levator palpebrae superioris; 5, rectus muscle; 6, cornea.

to the fatty degeneration of the recti muscles of the orbita, and for Müller's theory claiming that exophthalmos is due to a serous infiltration of the retrobulbar connective and fatty tissues of the orbita on account of vasomotor disturbances caused by thyrotoxicosis. If this edema should really exist, there would be no reason why it should not extend to the eyelids. It is true that sometimes edema of the eyelids is found in Graves's disease, but this is far from constant. Furthermore, these different theories are not at all supported by the findings of post-mortems which have been made by a number of authors and myself. Macroscopical as well as microscopical examination of the entire orbita failed to reveal either an excess of fat, an edema, a passive congestion

or a fatty degeneration of the recti muscles. Furthermore, such theories do not permit one to understand intelligently the rapid fluctuations seen in exophthalmos. These theories do not suit. Some other explanation must be found.

In 1858 Heinrich Müller described a layer of unstriped musculature located in the inferior portion of the orbita, and in the following year he described another layer in the superior portion of the orbita; this muscle has since been known as Müller's muscle. In the upper lid it is formed by a thin layer of unstriped muscular fibers running (Fig. 75) from the terminal palpebral insertion of the musculus levator palpebræ superioris to the upper convex border of the tarsal cartilage, into which it terminates directly, or through the means of elastic fibers. This muscular layer is about 10 millimeters in length and of varying thickness. In the lower lid these unstriped muscular fibers extend from the conjunctival fornix to the border of the lower tarsal cartilage. The description of this muscle has been reviewed by many authors, as Sappey, Testut, Merkel and others, and found correct. This muscle has no direct relation whatsoever to the eyeball. It is an *eyelid muscle*: it will consequently be easy to understand that this thin muscle can have no effect whatsoever upon the globus oculi, therefore any theory holding that this muscle is the cause of exophthalmos must fall. It can produce eyelid symptoms, but not exophthalmos.

Graefe, Sattler and McKenzie have thought that exophthalmos might be caused by an intense active and passive venous congestion of the orbita. As said before, postmortems failed to show any support for this theory. Furthermore, if this were true, we should expect to find this passive as well as active congestion confined, not only to the orbita itself, but also to the veins in direct communication with the orbital veins, through the nasofrontal and supra-orbital veins communicating with the ophthalmic veins. There should be, too, a venous stasis of the retina. But there are no such things.

Many authors, as Fuchs, Mannheim, Krause, A. Kocher and others, have sought to explain exophthalmos by claiming that there was a marked dilatation of all the arteries of the orbita, caused by the thyrotoxic condition, and possibly through direct stimulation of the sympathetic nerve. As Landström rightfully remarks, this theory is hardly acceptable. It is scarcely conceivable that we should have such a localized arterial dilatation so developed as to cause sometimes, not only a marked exophthalmos, but even a dislocation of the globus oculi. If such were the case, we should certainly expect to find a pulsating exophthalmos, which even in the most pronounced cases is never observed.

Landström thought that he had solved the problem when he described a new unstriped muscle. In making seriated microscopical slides of

the entire content of the orbita, he demonstrated the existence of unstriped fibers taking their origin in the septum orbitale, and taking their insertion on the equator of the globus oculi. This muscle forms a shallow cone which holds the eyeball in suspension. According to this same author, since this unstriped musculature is supplied by the sympathetic nerve, the explanation of exophthalmos is a clear one. It is due, he thinks, to a constant permanent contraction of Landström's muscle on account of the permanent thyrotoxic excitation of the sympathetic nerve. Certainly this theory is one of the most satisfactory ever advanced. But, although it may explain the mild cases of exophthalmos, it nevertheless fails to give a satisfactory explanation for the cases in which protrusion of the eyes is so marked as to cause dislocation of the eyeball. Under such conditions Landström's muscle cannot be considered as an etiological factor, because, since it takes its origin on the septum orbitale and its insertion on the equator of the eyeball, it would be able to lift the eye out of the orbita only as far as the level septum orbitale and no farther. The portion of the eye behind the equator oculi still remains in the orbita. There must consequently be some other factors which still remain to be discovered.

The problem would be solved if any musculature had been found in Ténon's capsule. This, to my knowledge, has not been demonstrated. If it were, since Ténon's capsule is indirectly attached to the septum orbitale through the fibrous expansion of the striped muscles of the orbita, it would then be easy to understand that any contraction of this membrane would throw the eyeball forward. Furthermore, there would be no difficulty in explaining any degree of exophthalmos up to dislocation of the eyeball. This, however, still remains to be demonstrated.

That the sympathetic intervenes as an active and potent factor in the production of exophthalmos there can be no doubt. Claude Bernard and many authors have shown that the excitation of the cervical portion of the sympathetic produces an enlargement of the palpebral fissure and exophthalmos. It has been said that exophthalmos is due to the mechanical irritation of the sympathetic nerve by the hyperplastic goiter. Although this might be possibly true in some cases, we must say, however, that if hyperplasia of the thyroid in itself plays a mechanical part by irritating the sympathetic nerve, this part must be a small one, and is not a constant one, since the relief afforded to the ocular symptoms by lobectomy or ligation is, although sometimes striking and occurring as soon as the operation is performed, only temporary, as a rule. Usually, one, two or three days after the operation, exophthalmos returns to its previous intensity. It is true that the supposedly mechanical irritant still remains *in situ* after ligation, but even when it has been removed, as after thyroidectomy, the ocular symptoms are



nevertheless still present. Furthermore, large, simple, malignant and inflammatory goiters, tumors of the cervical lymph nodes, very seldom produce any mechanical involvement of the sympathetic nerve. Why should the thyrotoxic goiter alone have that privilege? The truth of the matter is that the thyrotoxic poison acts electively upon the sympathetic system, thus acting as an irritant. The sympathetic disturbances are, however, in the great majority of cases, secondary and not primary, as some internists like to believe.

One thing still remains to be explained: Why is it, that even after all the other thyrotoxic symptoms have subsided, exophthalmos still persists for a long time, and sometimes for good? Most likely because the eyeball having been protruded for so long a time has lost its "right of domicile" in the orbita: it has acquired new relationships: connective tissue and, at times, retrobulbar fat have filled the dead space left by the eyeball when protruding, hence the difficulty or even impossibility for the *globus oculi* ever to return to its previous normal anatomy.

The Graefe, Kocher and Dallymple symptoms are easily explained; they are due to the irritation of the sympathetic nerve which supplies Müller's muscle. As seen before, this thin layer of unstriated musculature in the upper lid extends from the termination of the levator palpebræ to the upper border of the tarsal cartilage; in the lower lid it extends from the conjunctival fornix to the tarsus. Consequently, the contraction of these two little muscles will retract both eyelids and will enlarge the palpebral fissure; it will explain, too, the cramp-like retraction of the eyelids. Possibly, Sattler's explanation of the Graefe symptom may be partly true also. He claims that it is due to incoördination between the centers of the *musculus levator palpebræ superioris* and those commanding the up-and-down movements of the *globus oculi*. This theory, of course, would explain the incoördination between these two movements, but would not explain the sudden retraction which often takes place in the upper eyelid while the *globus oculi* is rolling downward.

It has been said that the eyelid symptoms are caused by an exaggerated tonus of the *musculus levator palpebræ superioris*. I fail to see why we should have an increased tonicity of this unstriated muscle alone, when we all know that in Graves's disease the striped musculature is anything but braced up: the sudden giving way of the knees is the best proof of that. In my judgment the *orbicularis palpebræ* does not play any part in the production of eyelid symptoms.

## CHAPTER XXIV.

### MUSCULAR SYMPTOMS.

AMONG the main muscular symptoms observed in Graves's disease are: *tremor, great muscular fatigue, sudden giving way of the knees, paresis and paralysis.*

**Tremor.**—Already observed by Charcot, in 1863, tremor was carefully studied later by Marie, and considered by him as one of the cardinal symptoms of Graves's disease. Tremor is not always noticeable externally and patients often describe their own consciousness of tremor as an "inward trembling"; in marked cases, they are, so to speak, in continuous vibration. Tremor may be localized or general. It may be localized to the upper extremities only, being then much more marked in the hands and extended fingers; it may even be more developed in one side than in the other, while in rare instances, it may be, or may become unilateral. In the lower extremities it is best seen when the legs are stretched out. In rare instances, tremor extends all over the body. It may involve the tongue, too; in that case fine fibrillary contractions are seen when the patient is asked to protrude his tongue. The tremor may be observed in the lips when tightly closed. When only half-shut the eyelids may show some tremor which may become more accentuated when the eyelids are more tightly closed; this is known as the Rosenbach symptom. This symptom, however, is not pathognomonic of Graves's disease as it is often found in neurasthenia and other nervous conditions.

Tremor is perhaps one of the earliest symptoms found in Graves's disease. It may be present for months before the disease is fully developed. It is best perceived while the patient is sitting or standing with outstretched arms, and it becomes less marked in the lying posture. Tremor, just as with the other thyrotoxic symptoms, is variable in intensity, and may disappear for a certain period of time and then appear again. According to Sattler, who went over the literature of the subject very carefully, tremor is present in 9 per cent of all the cases of Basedow's disease.

The chief characteristic of the thyrotoxic tremor is its exceeding fineness. The oscillations are frequent and of uniform rhythm, from 7 to 10 per second; the amplitude of these oscillations is small. The fine tremor seen in Graves's disease resembles in its amplitude of excur-

sion, rhythm and frequency the tremor which is seen in normal individuals, with this difference, however, that in normal individuals the tremor is so scarcely noticeable to the naked eye that it requires the graphometer to bring it out. This has been beautifully shown by Sattler. The tremor seen in normal individuals after great shock, violent psychic emotion, is of the same character as the one seen in Graves's disease.

Tremor is not pathognomonic of Graves's disease, since it is also found in various nervous diseases. The thyrotoxic tremor has a smaller amplitude than the one seen in paralysis agitans, but is faster. It is faster, too, than the senile tremor. It resembles the tremor seen in hysteria, in traumatic neurosis and in alcoholism. Besides tremor there are sometimes observed in Graves's disease jerky, involuntary movements, especially of the head and extremities, reminding one of chorea.

**Great Muscular Fatigue.**—Great muscular fatigue is a frequent accompaniment of Graves's disease. Spells of fatigue, or *asthenic crises*, of very mild type, are frequently seen in normal individuals. How often do we not hear normal individuals say, "I am all in today," or "I don't feel up to the mark!" Yet, there is no apparent cause for that state. I do not think there is an individual who is so normal, so well-balanced, as to enjoy uninterrupted perfect physical, moral and intellectual equilibrium. Everyone has his ups and downs, no matter how mild they are. These spells of lassitude are, as a rule, purely physical. They come on without any apparent cause; last probably a few days and then disappear as they came without any apparent reason for them. These asthenic spells are characterized by a more or less complete reluctance to physical effort: the least exertion seems to tire immensely. Otherwise the individual is all right. He may possibly complain of some intellectual laziness, or of some diminution of sexual appetite, but that is all. As soon as the spell is over the individual feels all right again. These spells may recur two or three times a year, and sometimes more frequently. Changes in the weather and in seasons are often considered as a cause of them, hence the terms "spring fever," etc.

These spells, mild and capricious in nature, are likely due to some rupture in the equilibrium existing between the glands of internal secretion. The best proof for this is that they are successfully combated with extracts from the endocrine glands, as the thyroid, pituitary body, adrenals, ovarian and testicular extracts.

These asthenic spells, which are barely sketched in normal individuals and without any pathological ground for them, we find extremely marked in Basedow patients. They may reach an extreme degree of intensity and last over periods of months, sometimes of years. This sense of extreme fatigue is not relieved by rest in bed, because in the

morning the patient rises as tired, if not more tired than he was when he went to bed. The weakness involves the entire musculature. Measured with the dynamometer, the muscular strength shows considerable diminution. In some instances physical effort has become so repugnant that the patient lies motionless in bed, even refusing to perform the most necessary movements necessitated by feeding, etc.

How can we explain this muscular hypotonus? Very likely, through some interference with the function of the suprarenal bodies. We are warranted in assuming that their cortical cells, the *spongiocytes*, are entrusted with the duty of neutralizing the muscular toxins, and that the medullary cells, the *chromaffin cells*, produce adrenalin whose tonic action, especially upon the circulatory and muscular systems, is well known. On the other hand, it is more than probable that the thyroid secretion is antagonistic to that of the suprarenal bodies. In hyperthyroidism this antagonistic action will be pushed to the maximum, especially if the case is complicated with thymus hyperplasia, since we know that the thymus is, most likely, another antagonist of the adrenal glands. Most likely too, other organs of internal secretion intervene also. Consequently, if we sum up all these influences we must expect a marked adrenal insufficiency. In fact, that is just what happens. A number of postmortems of cases of Graves's disease have shown that the size of the adrenal glands was materially reduced.

**Sudden Giving Way of the Knees.**—One symptom which is quite often seen in Graves's disease is the sudden giving way of the knees. This occurs without any warning, without any vertigo; the patient suddenly drops as if his legs were cut away from under him. It is most likely to occur when the patient is going down stairs, or when he is in a hurry to catch a car, or in some activity of that kind. The patient often has difficulty in getting up without aid; sometimes he cannot do so at all.

**Paresis and Paralysis.**—Once in a while the muscular hypotonus becomes so marked as to cause true muscular *paresis* and *paralysis*, as is shown by the paralysis of the frontal muscle; as a consequence of it the forehead does not wrinkle but remains motionless.

**Muscular Cramps.**—Muscular cramps occur once in a while in conjunction with Graves's disease. They are mostly localized in the calf of the leg and occur during the night. Cramps in the arms and hands, somewhat tetaniform in character, have been observed very rarely.

**Tendinous Reflexes.**—In the majority of true exophthalmic goiters it can be said that the tendinous reflexes are rather exaggerated. They may be, however, normal, diminished or even non-existent.



## CHAPTER XXV.

### NERVOUS AND MENTAL SYMPTOMS IN BASEDOW'S DISEASE.

BROADLY speaking, more or less all of the clinical symptoms seen in Graves's disease occur through the sometimes primary, more often secondary involvement of the nervous system governing the vegetative life. In *sensu strictiori*, however, there are symptoms which are more than others directly due to some disturbances of the nervous system. These are the symptoms which we are going to study in this chapter.

The chief nervous characteristics seen in Basedow's disease are: *emotionality, irritability, restlessness and instability*. More severe cerebral disturbances may also be observed such as obsessions, impulsions, hallucinations and mental confusion. True insanity may even be encountered.

Basedow patients are, above all, *emotional*. The slightest cause will throw them into a wild state of excitement which goes hand in hand with an exacerbation of their physical state. As Peter has said, "Basedow patients can be compared in every respect to normal individuals subjected to great excitement." In both conditions anxiety, palpitation, tremor, secretory disturbances, such as perspiration, diarrhea and polyuria, etc., are present. Some Basedow patients are afflicted with a pathological sensitiveness; they laugh and cry apparently without the slightest cause. Some of them have fits of religious mysticism, some others show abnormal excitation of the sexual apparatus, while others live in a state of constant fear. I recall a patient who developed a marked mania for music. Although devoid of any special musical gift, whenever she heard music she would plunge herself into a semicataleptic state, recoiling within herself, with a fixed and staring look, tense and vibrating. One would have thought that she was enjoying a paroxysm of artistic sensations. Possibly she was, yet there was always in my mind a suspicion that a great deal of it was simply affected. This fact should not diminish at all the interest in the observation, inasmuch as simulation and deceit are among the features of certain hysterical derangements. I recall another patient who developed a sudden morbid passion for cards. In conclusion it may be said that the emotionality in Graves's disease is nearly always exaggerated and consequently pathological.

Some thyrotoxic patients become exceedingly *irritable*. They may enter into the most paroxysmic fits of rage. Trousseau has said that some Basedow patients live in a state of perpetual anger. Although possibly of quiet, nice, self-possessed disposition previous to the outbreak of the disease, these patients become difficult to handle. They quarrel with their most intimate friends, and render life miserable for the members of their families. Their love for their own relatives becomes less and less marked; they think only of themselves and become extremely and peculiarly egotistical. They require the most constant attention, and even when the most devoted care is given them they complain of being neglected. Gradually their love changes into hate. This frame of mind will explain why a great number of these patients are divorced or separated women, and why some of them are simply abandoned by their husbands. Of course this is no excuse for the husband's cowardly act, but may explain it to a certain extent. Too often, I am sure, the husband does not realize that his wife's bad temper is pathological, that she should be treated as a sick woman, but rather takes it for granted that his wife has an infernal disposition, and that both will be better off separated.

The mental condition in Basedow's disease is most *restless* and *unstable*; it varies with the degree of excitation or depression in which the patient finds himself. If he is undergoing a period of excitation, his intelligence is vivid and excessively mobile. The patient will spend hours in thinking and scheming, and will translate his exaggerated mental activity into a profuse loquacity, talking about everything in the most superficial way, and jumping from one subject to another without the slightest effort. If I may be allowed to use a metaphor, he is suffering from a veritable "cerebral diarrhea." Usually the memory is good. With this exaggerated mental activity there goes hand in hand an increased physical activity. The Basedow patient is exceedingly restless, constantly moving, and changing position. He is unable to remain seated very long at a time, but goes and comes, sits and rises, and makes hasty movements—many of them involuntary and without purpose. The patient shows considerable ardor in the accomplishment of the various tasks he undertakes, but as he is mentally unstable, he seldom terminates what he starts out to do. He will tackle one job after another, but will not accomplish much; in short, he shows an incoherent activity without any definite purpose.

In other patients, on the contrary, we find mental depression; they cannot concentrate their attention upon any subject without the greatest fatigue. Their memories are weak and untrue. There is a marked intellectual laziness which prevents them from pursuing a train of ideas. At the same time there exists a more or less complete physical

apathy. Since their mental faculties are depressed and their physical needs are reduced in the same proportion, these patients will lie motionless in bed, every physical effort being distasteful, even painful to them.

In some toxic cases, especially in those of the non-exophthalmic type, the mental picture is rather one of depression minus delusions. These conditions are distinguishable from the non-endocrine neurasthenoid states by means of the study of basal metabolism and by the adrenalin test.

In conclusion we may repeat what we said in the beginning of this chapter: the nervous and mental state in exophthalmic goiter is characterized by *emotionality*, *irritability*, *restlessness* and *instability*. These pathological features are subject to great variations; they improve as the thyrotoxicosis subsides, and, *vice versa*, they become more marked as the thyrotoxic condition gets worse.

In the late stage of the disease these psychic disturbances may acquire a more serious character.

Not so infrequently the exophthalmic goiter will terminate by an *acute delirium*. This delirium resembles in every respect the one seen after intoxication with iodoform and in postoperative hyperthyroidism. In all three conditions the patient shows an extreme agitation and is delirious; he does not recognize his attendants any longer, nor the members of his family; he wants to get rid of his covers, his dressings, to get out of bed, and almost invariably, he "wants to go home." Sometimes it takes several nurses to hold him in bed. He talks constantly in a more or less incoherent manner about those things which are familiar to him, especially those of his occupation or profession. If he is a farmer, he may talk about pitching hay; if he is a lawyer, he may talk about defending a suit; if the patient is a housekeeper, about some feature of housekeeping. This delirium, however, is not systematized. It is usually accompanied by hallucinations. Then the patient speaks to people whom he sees in his delirium dreams; they may stand beside him or on his bed; they may be at the threshold of the room, or perhaps climbing over the window. Not infrequently one will gather from what the patient says that the people whom he sees want to do him harm, that they want to kill him.

This form of delirium may last for days and weeks, and usually terminates in death. That this form of delirium is in direct etiological relation to thyrotoxicosis there can be no doubt. As said before, it resembles so closely the one seen in certain forms of postoperative hyperthyroidism that its etiology must be the same.

There are, however, a number of psychoses which occur in conjunction with Graves's disease whose etiological relation is still an open question for discussion. I have in mind those transitory obsessions and

impulsions which are sometimes seen in Basedow's disease. In 1871, Solbrig reported the case of a woman, who, although deeply loving her children, wanted to kill them. I have seen a similar case. It was that of a woman who felt at times an irresistible impulse to kill her child. A patient of Raymond and Serieux was afraid to cross a large public square because she thought that she was bound to be run over by a wagon. Another patient thought that she was going to die, that her heart was going to burst, or that something was going to fall upon her and crush her. Some patients have a tendency to suicide, and a patient of Plaignard constantly saw herself hanging to a window. All these obsessions, impulsions and phobia have the peculiarity of being irresistible, or at least of being filled with the utmost anxiety. The obsession is sometimes so intense that on the spur of it the patient will occasionally do the most extravagant things, and the most cruel thing of all is that he knows that his impulses are wrong, so that for a long time he will fight against them; hence the great moral and mental suffering which terminates only when the impulsive act, no matter how extravagant or immoral, has been accomplished. Although he knows that he acted wrongly, nevertheless he feels a sense of relief and satisfaction, temporary at least, when the act has terminated the crisis.

Exophthalmic goiter may occur as a complication in a variety of psychoses such as in pseudosystematized delirium of degenerates, in mania, in melancholia, in maniacal states, in depressive melancholia, in delirium acutum, in paranoia, etc. *Vice versa*, psychoses may follow after Graves's disease has long been fully developed. Psychoses may occur at any period of the development of Graves's disease. Sometimes only after the thyrotoxic complex has subsided entirely do we see the development of psychoses. On the other hand, the goiter may appear years after the patient has had psychic disturbances, and which have long since subsided.

That *hysteria* may be found in combination with Graves's disease cannot be denied. It is a complication seen more often in young women than in men, and it may develop later as a complication of Graves's disease. As a rule, however, when hysteria is present it has existed before Basedow's disease underwent its development.

Tanzi writes: "Cases of exophthalmic goiter which present hysterical phenomena should be regarded as latent hysteria brought to the surface by exophthalmic goiter. It is the hyperthyroidism which evokes the syndrome. Because of the associated symptoms of exophthalmic goiter we can clearly determine that it is the thyroid toxin which has initiated the hysteria, just as it initiates the sensitiveness, the depression and anxiety which are common manifestations of thyroid disease. There may have been susceptibility to acquire hysteria, but this does not nega-



tive the fact that the hysteria has been manifested through the external determinant, the thyroid toxin."

That hysteria is an entity by itself is shown by the fact that it does not follow the course of Graves's disease, improving when the latter improves and getting worse when the other undergoes exacerbations. The hysterical symptoms may follow their course, getting worse while the thyrotoxic symptoms gradually disappear.

It would be a mistake, however, to believe that the majority of Basedow patients are hysterical; this is not so. In my own experience, I would say that the majority of patients do not show the characteristic mental accompaniments of hysteria. As Thomson says: "They look their physician straight in the face, and show no response to suggestions. They deny the symptoms which they do not have, and remain consistent in their description of the symptoms which they have, with no variation in their story for months, while they are always ready to acknowledge any improvement in their symptoms when they occur."

*Neurasthenia* sometimes occurs as a complication of Graves's disease; it is more frequent in men than in women. Like hysteria, it is not in direct relation to thyrotoxicosis, but seems to be a nervous disturbance *per se*.

We have, consequently, the right to ask ourselves the following question: Beside the acute delirium described above, is there a true thyrotoxic insanity, or are the psychoses found in conjunction with Graves's disease purely accidental? From all the well-authenticated cases reported in the literature which I have been able to lay my hand upon, it seems to me that we cannot consider these psychoses as of thyrotoxic origin. They are only associated nervous disturbances grafted upon a predisposed terrain. Here, too, we find the same burdened heredity, and the same psychic as well as physical stigmata found in the same psychoses complicated with Basedow's disease. From the grave and rapidly fatal cases of acute thyrotoxicosis to those marked by the syndrome of melancholia or mania, on through the milder manifestations, we have to do with physical symptoms which exist as secondary results of thyroid disturbances. That, however, Graves's disease supervening in such predisposed and unstable terrain is bound to favor the appearance of psychoses is a fact which everyone will readily admit. The reverse is true, too; thyrotoxicosis will evolve more easily and more fully in individuals whose nervous system is already in an unstable equilibrium. When I see certain young, nervous, irritable and unstable individuals, I cannot help but look upon them as future candidates for Graves's disease.

Let us study the mechanism by which these symptoms are brought about. We know that the cell-body represents the traffic center *par*

*excellence* of the neurone's mechanism and that upon it the activity of the nervous function depends. It is pretty generally known that infectious diseases, intoxication and metabolic disturbances of all sorts, act upon the nervous body cell to greater or lesser degree, causing most likely nutritive as well as circulatory disturbances resulting finally in a defective metabolism of the nerve cell itself and of the neurone. Hence, loss of smooth functioning of the delicately constituted fibers. As Walker says, "The associate mechanism is thus prevented from performing its work properly; delays and interruptions occur along the associative tracts between areas of special sense perception; there results a feeling of strangeness and unreality, bewilderment, confusion and oppression, together with excitement or depression, sometimes wild illusions and hallucinations." The degree of involvement of the associative mechanism will be in direct relation to the mental clinical syndrome observed. If the involvement is severe, we shall observe these severe, acute and often fatal cases of mental derangements that we have described above. They offer the clinical picture of total amentia, acute mania, etc. In the less spectacular mental symptoms we shall find these transitory attacks of excitement with confusion or delirium very similar to the mental disturbances observed in infectious diseases, such as pneumonia, typhoid fever, puerperium, etc. As in the toxins of infectious diseases, so here, "The thyroid toxin not only endangers the vitality of the nerve elements, but may also elevate or depress their condition of excitability; and the effects of such stimulation or depression may be combined in a great variety of ways."

Moods of depression and anxiety, fits of overstimulation, attacks of suspicious attitudes, with mild delusions rooted in a clouding of consciousness; morbid ideas associated with feelings of injury, jealousy, shame, fear and anxiety of the obsessive type; hallucinatory and persecutory states; impulsive obsessions and acts; weakness of memory and attention; exaggerated emotional tonus of the individual; irritability, indecisions, quarrelsome tendencies, incapacity for continuous mental application; all these phenomena with a varied shading, almost *ad infinitum*, recognize the same and sole cause, namely, the nocive influence of the thyroid toxin upon an already predisposed nervous system, finally resulting in disturbed circulation, disturbed metabolism, and in states of depressed or overstimulated function of the nerve cells. As a result, the mental, motor and trophic nerve centers lose their coördinative and sensitive power, and if the disturbance lasts long enough, the consequent impairment of the great regulative and cortical system will undergo steady deterioration, thus rendering the patient a mental and physical wreck.

Microscopical findings in such cases show evidences of work exhaus-

tion, translated by hyperchromatism and chromatolysis of the cerebral, cerebellar and medullary cells. These findings do not differ in any way from those found by Crile in patients who died from thyrotoxicosis. They, too, are very similar to the ones found in patients who died from long-standing intoxication and exhaustive processes accompanied by mental disturbances.

Thyrotoxic psychoses not only illustrate the importance of the toxic factor in the pathogenesis of psychic symptoms, but they further emphasize the fact that the "brain, which is extremely sensitive to all poisons, reacts to those which are produced within the organism not less intensely than to those which are derived from the outside."

In the domain of cerebral nerves, *palsies* are not so uncommon in thyrotoxicosis. All other nerves have been found involved in this disease with the exception possibly of the nervus accessory. The nerves supplying the eye muscles are the most frequently involved, namely, the oculomotor, the trochlearis and the abducens.

Kappi, in 1911, collected about 40 cases in which ophthalmoplegias of varying degrees were encountered in thyrotoxicosis with the absence of any other involvement of the cerebral nerves. Isolated palsies of the facial nerve are not frequent. Sattler, in 1909, reviewed the literature on the subject very completely.

In the domain of the cerebral nerves we find sometimes palsies simulating very closely an acute or subacute or chronic bulbar paralysis. In such cases it is not always easy to differentiate cases of "bulbar paralysis with anatomical lesion" from the cases of "bulbar paralysis without anatomical lesion."

*Chorea and choreiform* conditions are sometimes seen in conjunction with Graves's disease. I, myself, have met with that combination several times. It occurs nearly always in young girls and children. There is no definite relation between the two conditions as to their onset; chorea may develop first, and then the exophthalmic goiter, or *vice versa*, or the two conditions may develop at the same time, or one of them may regress while the other remains progressive. As a rule, however, the improvement of one involves the betterment of the other. Although their association is purely accidental, there appears to be in certain instances an etiological relation.

**Neuro-circulatory Asthenia.**—During the past war the number of men at and behind the front, incapacitated by a condition regarded as having been caused by explosion of shells, continuous firing, excessive fatigue, mental as well as physical, was quite an important item, which at times taxed to the limit the housing capacities of the improvised hospitals. Thus, as reported by Col. Pierce Bailey, France maintained 20,000 neurological beds in the rear and at the front and tried to

maintain one and one-half neurological beds for each 1000 troops. According to Major Arthur Hurot, R.A.M.C., Great Britain devoted 26,000 beds to this purpose.

In the beginning most of these neurological patients were regarded as "shell-shocked." Later this denomination was extended not only to the soldiers who had seen actual fire, but to those in the rear where gunfire, shell explosions, etc., could not be regarded as the etiological factor. Finally, patients coming from civilian life who offered the same syndrome were labeled in the same way. This was done because the syndrome presented by all the patients was about the same.

It was soon found out, however, that men in training camps, away from the battlefields, offered a clinical picture resembling the one of shell-shock. It was called in turn, "irritable heart," "soldier's heart," "war tachycardia," "neurocirculatory asthenia," "soldier's psychoses," "neurasthenia," "hysteria," "early tuberculosis," all terms employed as a cloak for the lack of understanding as to the real clinical and pathological entity of the condition. It was only by grouping the clinical data gathered by medical observers in all the armies that a clearer understanding of the condition was finally obtained. When this was done, it was soon found that the great majority of these cases labeled "shell-shock," "irritable heart," and so forth were conditions developed on a thyrotoxic basis. A remaining small number could not be classified, since in such cases the thyroid seemed to be absolutely foreign to the pathological condition observed, but the most of them belonged to the great class of insane such as melancholia, acute mania, dementia precox, etc., all conditions whose real etiology is unknown. As often is apparent in civilian life, here, too, heredity seemed to play an important role as a predisposing factor.

So far as another large class of shell-shocked patients is concerned, if we put together the mass of evidence reported by a number of observers, there can be no doubt that the thyroid appears to be the dominant etiological factor. Thus, F. D. Smith, reporting 116 cases of toxic goiter discovered among 65,507 men examined at Jefferson Barracks, comes to the conclusion that physical as well as mental strain in such cases may be regarded as responsible for the explosion of a hitherto latent, incipient hyperthyroidism. I. Barr is of the same opinion. Wilson observed thyroid hyperplasia in about one-ninth of his cases and noticed, furthermore, that thyroid medication made the condition worse. Poynton and Stoney regard, too, the "soldier's heart" as of thyroid origin. Hernanan-Johnson and White regard the "irritable heart" as a form of thyrotoxicosis. K. W. Ney in his report on military surgery considers these cases of "shell-shock" sent back from the firing line as mostly due to some derangement of the endocrine glands, especially the thyroid, through a



disturbance of the emotional balance. Harlow Brooks at Camp Upton Base Hospital concluded that the neuroses described as "shell-shock," "irritable heart," and other allied terms are all, in some way or another, forms of hyperthyroidism. He says that tachycardia and palpitation were the chief complaints. Cardiac action, as we know, is increased by physical as well as by emotional strain. Functional murmurs over the cardiac area, especially at the apex, were often detected. Throbbing of the cervical bloodvessels and frequently of the aorta were also observed and soldiers frequently complained of precordial distress. Vasomotor instability was evidenced by flushing of the skin, dermographism, etc. Tremor with fine oscillations was almost constant. Patients complained of insomnia, were very nervous, showed outbursts of emotionalism, of temper, and had unmotivated crying spells. In Brooks's cases two-thirds of the soldiers had some degree of thyroid hyperplasia. Even exophthalmos was present in some cases. He furthermore observed that tobacco and nitrites had a detrimental effect upon the patients. In these cases the adrenalin test was applied as a routine laboratory examination.

Such a description as that just recounted could not tally better with the description of thyrotoxic cases that we see in civilian life. We are consequently forced to admit the same etiology in both conditions, namely, the thyroid. Physical as well as mental strain, environmental and emotional tension, seem to be the cause for the explosion of a hitherto quiescent, unrecognized hyperthyroidism into cases of greater magnitude. Most of the observers were unanimous in stating that in most of these cases, familial goiter, nervous instability, hysteria, insanity, and the like, were indicated. So that here, again, we are forced to conclude that emotion, fear, fright, etc., are not to be regarded, at least in the majority of cases, as the *primary* causative factor, but only as the *secondary* one, the primary cause being an already *latent, unrecognized thyroid disturbance*. And obviously it must be so. If it were otherwise, how are we to explain the fact that only a small percentage of the men submitted to the same ordeal developed thyrotoxicosis while the great majority did not?

**Heredity of Graves's Disease (Familial Thyrotoxicosis).**—That Graves's disease may be hereditary is shown by a number of examples. In 1884, thyrotoxic goiter was reported to be present in 16 members of the same family. Osterreicher reported the case of a hysterical woman who had 10 children, 6 girls and 4 boys. Eight of these children developed Graves's disease. One of the daughters married and had 4 children; 3 of her daughters developed exophthalmic goiter and the fourth was hysterical. Cantilena reported the case of a hysterical woman having 2 children, 1 son and 1 daughter; both had exophthalmic goiter. The daughter herself had 3 girls, two of whom developed exophthalmic goiter. Cheadle saw 4 cases of exophthalmic goiter in the same family. Thyssen reported

a case of a mother and daughter having exophthalmic goiter. Solbrig and Kronthal also reported a case of mother and child having exophthalmic goiter. Dejerine saw a family in which exophthalmic goiter was hereditary during four generations. Souques and Lermoyez, in 1918, reported a case of familial thyrotoxic goiter in which there had been 7 cases of exophthalmic goiter among the 16 members of the family in three generations. I have seen 3 sisters afflicted with exophthalmic goiter; in another instance a mother and her daughter both had exophthalmic goiter. Similar cases are not so rare. It is not so infrequent to see Graves's disease develop in patients whose nervous heredity is heavy. Familial thyrotoxic goiter is consequently not very rare.

## CHAPTER XXVI.

### DIGESTIVE DISTURBANCES.

DIGESTIVE disturbances are very frequent in Graves's disease, and their importance is not to be belittled, because they will often so interfere with nutrition that life is endangered. None of the symptoms seen in Graves's disease seems to tell upon the general condition of the patient so much and so quickly as gastro-intestinal disturbances. In a very short time the patient will melt away, and in a few weeks may be dead. We have all seen these fulminating forms of thyrotoxic troubles which in less than six to ten weeks have brought a Basedow patient, whose general condition at the onset was otherwise good, to his death.

The first fact to note is, that these symptoms develop usually when the disease is in its incipency. A number of times they will be found in the history of the patient so long before any of the thyrotoxic symptoms have been clearly established, that we may say that they are often the forerunner of the disease. This is especially true for diarrhea; hence the necessity of always bearing in mind the possibility of Basedow in cases where diarrhea sets in without apparent cause, remains persistent for a while and then subsides.

The other fact is that digestive disturbances are *distinctly specific*, and manifestly unlike any other affections of the gastro-intestinal tract. In their mode of appearance, in their pathological manifestations, and in their way of subsiding they are always the same. They usually occur without any apparent cause and subside the same way. They sometimes appear to follow a cycle. With their paroxysmal character and with their peculiar way of appearing and subsiding, they remind one of tabetic crises. Never at any stage of their development, may it be at the beginning or the end, do they present the inflammatory, exudative, or ulcerative characters seen in other pathological conditions of the gastro-intestinal tract.

Finally, they are most *uncontrollable* and stubbornly resist any form of medical treatment, no matter at what stage of their development it may be instituted. That there is a close relation between the disturbances of the gastro-intestinal tract and the other thyrotoxic symptoms is shown by the fact that the course of the latter goes hand in hand with the improvement or exacerbation of the former. One thing is certain: no improvement in the disease can be expected so long as the gastro-

intestinal symptoms have not subsided. On the other hand, when once they have retroceded entirely, it is remarkable to see how quickly a patient will rally and put on flesh, even when his condition was such as to appear hopeless.

Another distinctive feature of these gastro-intestinal disturbances is the *acetone breath* which one will so often notice while near the patient, or even upon entering the room. It is due to *acidosis*.

Let us take these gastro-intestinal symptoms separately and study them.

**Appetite.**—Loss of appetite is very common and one of the early symptoms. It may be so marked as to lead the patient into a state of complete *anorexia*. I have seen fatal cases which for weeks showed an absolute repulsion toward food of any sort. In these cases if anorexia is complicated with gastric intolerance, if one succeeds in getting some food into the patient's stomach, that nourishment comes up again as quickly as it went down. In some instances loss of appetite alternates with spells of hunger. In other conditions the patient may suffer from *bulimia*; the appetite is then ravenous and never satisfied no matter how much food the patient takes. Bulimia often becomes intense during the night. It may even exist despite the most intense vomiting, diarrhea and loss of flesh.

**Nausea.**—A very common thyrotoxic disturbance is *nausea*. It is a very persistent and very annoying symptom which may last for weeks, months or even years, with or without periods of remission. It is usually more marked after eating, but may have no relation whatsoever to food, occurring as often with an empty stomach as it does after meals. Nausea is always worse in the morning; it rarely leads to vomiting.

**Gastric Flatulence.**—This is another symptom which often goes with the gastro-intestinal disturbances in Graves's disease; it has a most persistent character. The patients attempt to relieve themselves by frequent eructations which have none of the acid or acrid characteristics seen in other gastric disturbances. It seems to be mostly air which they eructate. This would lead to the belief that some of the patients are *aërophages* or *air-suckers*.

**Vomiting.**—In more serious gastric disturbances *vomiting* is always present. It may be so marked as to endanger the life of the patient. It occurs with an empty stomach as well as after taking food. When not too severe, it may take place only four or five times a day, while in severe conditions it may occur as often as ten to fifteen times a day. The vomitus may be watery, slimy or colored with bile; blood is very seldom found, but if it is, it is only under the form of some bloody streaks due very likely to injury of the mucous membrane of the stomach or esophagus through the efforts made in vomiting. As shown by repeated fluoro-



scopic examinations, the stomach is in a state of more or less constant spasticity.

Nothing definite is known about the *gastric chemistry* in hyperthyroidism and especially during the gastro-intestinal disturbances. As a rule there seems to be either anachlorhydria and apepsia, or hypochlorhydria and hypopepsia. In some instances, however, there is undoubtedly hyperchlorhydria.

**Diarrhea.**—Diarrhea is among the most important digestive disturbances in Graves's disease. Its running down effect upon the patient is possibly more marked than that of vomiting. Apparently without any precise cause, and usually in no relation to the taking of food, the patient will have a number of stools which may vary from 4 to 30 in twenty-four hours. These stools are watery, yellowish or gray in color, and often contain bile products. It is interesting to note that in certain cases the stools contain a great quantity of undigested fat. As a rule the discharges are not offensive and do not contain blood, mucus or pus. They are neither preceded nor followed by pain, although the patient may complain of a diffuse distress throughout the abdomen and of some flatulence. Like vomiting they show morning exacerbations. No medical treatment seems to have any hold upon them. Diarrhea may alternate with spells of *constipation*. Often, however, as soon as diarrhea has subsided, the intestinal tract resumes its normal function, just as if nothing had ever happened. If diarrhea is moderate and unaccompanied by vomiting, and if the appetite remains fair, its effect upon the patient will soon pass unnoticed. If, however, diarrhea becomes severe and is at the same time complicated with vomiting, the resistance of the patient will be put to a severe test.

In a few cases of very severe thyrotoxicosis, *icterus* may be observed. This icterus is rare, although it is not uncommon to observe a yellowish tint of the sclerotica in severe thyrotoxic gastro-intestinal disturbances. The prognosis of this icterus is always bad. This icterus is not due to any obstacle in the bile ducts, but is of toxic origin.

I think we are within our rights when we say that these gastro-intestinal symptoms are of vagal and sympathetic origin, secondary to some toxic influence of the thyroid secretion upon the sympathetico-vagal system.

## CHAPTER XXVII.

### GENITAL DISTURBANCES.

MENSTRUAL disturbances are quite frequently seen in conjunction with Basedow's disease. Although once in a while one may meet with a case in which menstruation is prolonged and profuse, as a rule, however, the opposite is true in the great majority of cases. In these menstruation becomes irregular, scant and often stops altogether for periods which may last months or even years. In some instances menstruation ceases abruptly long before any true symptoms of the disease show up. There is then a premature menopause which may remain permanent, no matter if it does occur a number of years before the natural time for menopause has come. I have seen thyrotoxic cases in which premature menopause occurred at twenty-eight, twenty-nine or thirty years of age, and which remained permanent after that. More frequently, however, menstrual disturbances develop gradually and in direct proportion to the severity of the disease. As soon, however, as the thyrotoxic condition begins to improve, menstruation gradually returns to its normal condition. The most hopeful sign in Graves's disease is the return of menstruation.

With the menstrual disturbances, there ceases, or at least, diminishes to a great extent, the sexual appetite; the entire genital apparatus undergoes atrophy and sclerosis; the uterus, tubes and ovaries become small. If the patient is a man the testicles undergo atrophy.

In conclusion we may say that in Graves's disease the entire genital apparatus is in a state of hypofunction.

Gynecological lesions, such as inflammations, tumors and malposition of the genital organs, are sometimes found in conjunction with Graves's disease. In some instances the surgical treatment of these gynecological lesions resulted in the absolute cure of the thyrotoxic symptoms.

## CHAPTER XXVIII.

### RESPIRATORY DISTURBANCES.

IN Graves's disease respiration certainly does not follow the same rhythm seen in normal individuals. It is rapid, superficial and irregular in character; it alternates with periods of rest which, in turn, are irregularly interrupted by one or two deep respirations which have more the character of a sigh: there exists a true respiratory arrhythmia. The number of respirations may attain the double of the normal number. Hofbauer, of Vienna, has shown that the respiratory curves in Graves's disease have a decided type of their own. The amplitude of their excursion is shorter than those seen in normal, and other pathological conditions; furthermore, inspiration and expiration are exactly equal in length; finally, these respiratory curves are irregular. Hofbauer claims that this type of curve is characteristic for Graves's disease, and that it is seen, not only in patients complaining of shortness of breath, but in the ones who apparently are not conscious of any respiratory trouble. Naturally, since short and superficial respiration will have as a corollary a diminished amplitude of the thoracic excursions, and since inspiration and expiration are of equal length, it follows that the excursions of the thorax during inspiration and expiration will be reduced in the same proportion. This can be easily demonstrated with a special apparatus for thoracic measurements, as was shown by Louise Fiske Bryson in 1889. This symptom has since then been known as the *Bryson symptom*.

**Shortness of Breath.**—Shortness of breath is often complained of by Basedow patients. It may be constant or may come on by spells. It may be present with or without physical exercise, but always becomes more marked when the patient does some exertion or undergoes some psychic excitement. This shortness of breath in the great majority of cases is not in relation at all to the volume of the thyroid. This might have been foreseen, as we all know that mechanical disturbances of the trachea do not cause a rapid and superficial respiration, but, on the contrary, that under such conditions respiration is slower and deeper. Might not this shortness of breath be of cardiac origin? It is true, indeed, that in certain advanced cases of hyperthyroidism we have marked cardiac disturbances due to vascular and valvular insufficiency. Under such conditions we shall have to admit that shortness of breath will be mostly due to cardiac troubles, but there again the respiratory

disturbances have a decided character of their own with which every one is familiar. Since shortness of breath is observed from the early beginning of the disease at the time when the cardiac muscle is still strong and its valves are still continent, we shall have to find something else than the heart to explain it. As we have seen, the cause of this shortness of breath is the disturbed rhythm of the respiratory apparatus itself. Respiration is superficial; the amplitude of the thorax is diminished materially, and consequently the intake of air is *ipso facto* reduced. These disturbances will naturally lead to insufficient oxygenation of the blood and will contribute toward increasing the already disturbed metabolism. But the true primary cause is most certainly in the direct influence of the thyrotoxin upon the respiratory centers. In advanced cases degeneration of the respiratory musculature, especially of the diaphragm, as has been shown by Askanazy, might be considered as an adjuvant factor.

**Coughing.**—A symptom which, when present, is persistent and annoying is coughing. The thyrotoxic cough is dry and not accompanied by expectoration; no pulmonary lesions are at the bottom of it. It is often exaggerated by the recumbent position, and becomes consequently annoying to the patient because it prevents him from sleeping. In the great majority of cases this coughing is not caused at all by the pressure of the goiter upon the trachea, but, according to Sattler, it is caused by an exaggerated sensibility of the mucous membrane of the entire respiratory apparatus. Under such conditions the irritant which in ordinary conditions would pass unnoticed is sufficient to produce a reflex cough. It must not be forgotten that many of these coughing spells are of hysterical origin.

**Hoarseness.**—Hoarseness without any definite pathological reason is seldom seen. *Weakness* of the voice, however, is much more frequent, and may sometimes lead to *aphonia*. The latter symptom is not in relation to the size or to the position of the goiter. Patients often complain at the same time of a sense of constriction in the throat, and sometimes accompanied by pain. These manifestations are nearly always of hysterical origin.



## CHAPTER XXIX.

### SENSORY DISTURBANCES AND INSOMNIA.

A SENSE of throbbing and tinnitus in the ears is sometimes complained of by Basedow patients. Rarely there is a disturbance in the sense of smell. As said previously, patients complain of pain in the eyes, of flashes of light and of dark and bright-colored spectra.

**Pains.**—Pains are among the most common complaints of Basedow patients. These pains are exceedingly variable as to their seat and nature. They may implicate such various parts of the body as the tips of the fingers or toes, the heels, the palms of the hands, the upper and lower extremities, and the joints, such as the knees, wrists and ankles. Often these pains are purely muscular. The most common site is in the muscles of the neck, especially the sternocleidomastoid muscles. These pains differ from rheumatic pains, since they are extremely shifting in character. They are not painful to firm palpation, do not show any swelling and are not materially affected by changes in the weather. They may be distinguished, too, from peripheral neuritis by their transient character.

**Headaches.**—Headaches are among the most frequent sensory disturbances observed in Graves's disease. Intermittent in character, they may be in some patients of almost daily occurrence. They are of the migrainous type. Sometimes they are periodical, occurring, for instance, at the menstrual periods. In the majority of cases they are characterized by the patient as "dull" headaches; sometimes they take the form of violent headaches. They are mostly localized in the occipital, the frontal, or the temporal regions, and are most frequently complained of in the morning. They are seldom accompanied by nausea or vomiting, and differ from typical attacks of migraine in not coming on in severe paroxysms and in not leading to vomiting.

It is self-evident that all patients suffering from headaches are not thyrotoxic patients. Since headaches occur with predilection in neuropathic individuals, it is fair to admit that Graves's disease will only exaggerate this neuropathic tendency, and, consequently, will increase the chances for headache; hence the frequency of the symptom. We might even go further and admit in certain conditions the existence of a *true thyrotoxic headache*, dull in nature, mostly localized in the occipital region, and subject to morning exacerbations. Often, too, headache is only a symptom of acidosis which frequently accompanies thyrotoxicosis.

**Vertigo.**—Occasionally vertigo is complained of by the patients. It is often associated with aural disturbances and is more pronounced in patients complaining of throbbing and tinnitus of the ears.

**Tingling and Numbness.**—Tingling and numbness of the upper and lower extremities is sometimes another complaint; it is more frequently observed in the lower limbs.

### INSOMNIA.

Another of the frequent complaints of Basedow's disease is *insomnia*. From a light sleep often interrupted by periods of wakefulness, up to a more or less complete insomnia, all degrees are seen. The patient may enjoy a few hours' sleep in the early part of the night, but after midnight insomnia becomes stubborn. Very often sleep is disturbed by dreams, more or less unpleasant, and which sometimes take the form of frightful nightmares.

## CHAPTER XXX.

### CUTANEOUS SYMPTOMS.

**Sensation of Heat.**—Vasomotory disturbances are quite frequent in Graves's disease; they manifest themselves commonly by an exaggerated sensation of heat. Basedow patients are always warm, in fact, too warm, although their bodily temperature is normal. When other people feel comfortably cool or, in fact, even cold, Basedow patients will still complain of being too warm; they seek drafts. During the coldest weather they feel comfortable only if the windows and doors are open. They wear only thin clothing, far too thin for a normal individual to be comfortable in. The winter is their best season, while in summer they always feel prostrated.

Basedow patients often complain of hot flashes; they flush easily and have red cheeks; the least physical or psychical excitation is sufficient to cause a marked congestion of the face and sometimes of the entire body.

**Dermographism.**—Dermographism is often found in Graves's disease. It takes its origin, too, in a disturbed vasomotory function. It may be obtained by scratching the skin once with a pencil or the finger. Two or three seconds after the scratching has been done, a red line, more or less intense, appears following the direction of the scratching; this line lasts quite a long time and then fades away. Not so infrequently instead of being red, the line is white; it becomes red only a little while after. In other instances the white line is surrounded on either side by a streak of red.

**Goose-flesh or Tricographism.**—This, according to Pende, is a very frequent phenomenon observed in thyrotoxic patients. This phenomenon is due to the contraction of the muscoli arrectores pilorum, which are controlled by the sympathetic system. When there is a mild irritability of the sympathetic system, stroking of the skin along the sternum or mammary region with a blunt point causes the "goose-flesh" to appear at once, not only in the zone above these structures, but also in all the surrounding region. This condition is due to irritation of the sympathetic.

**Hyperhydrosis.**—As a rule, Basedow patients suffer a great deal from hyperhydrosis. They sweat continuously and profusely, with or without any physical exercise, and very often at night as well as in the daytime. These sweatings, like the other thyrotoxic symptoms, are subject to great

variations, being more marked at times than at others. As a rule the sweat is odorless; however, in rare cases, a very offensive odor has been observed. On account of the constant moisture of the skin it will be easily understood, as Vigouroux has shown, why the skin of Basedow patients offers less resistance to the electrical current than the skin of normal individuals.

**Itching of the Skin.**—Not very frequent, but when present an annoying symptom, is itching of the skin. It may be accompanied by some skin eruption, but may be present, too, without any visible involvement of the skin. It may be exceedingly intense, may last night and day, and usually follows the up-and-down curves of the disease, improving when Graves's disease subsides, and getting worse when the disease undergoes exacerbations. This, however, is not always true. I have had recently under observation a patient whose thyrotoxic symptoms have almost entirely subsided, except exophthalmos and itching. Scratching neither relieves nor aggravates this itching.

**Urticaria.**—Basedow patients are apt to have skin eruptions. The most frequently seen is urticaria, which in some cases may be remarkably transient in character. I remember a case in which urticaria was so fugacious that it would disappear entirely in the time necessary for the patient to go from home to the doctor's office. This, however, is not frequent, and although very changeable in character, may nevertheless last for long periods of time.

**Falling of the Hair.**—The hair becomes dry, brittle, and falls out. The same is true of the nails of the fingers and toes. This occurs in the early beginning of the disease and retrocedes as soon as the condition of the patient improves. It may involve not only the hair of the head, but also that of the beard, and that over the different parts of the body, such as the arms, the thorax, and the axillary space; the eyebrows and eyelashes may even fall out. In all respects this falling resembles the loss of hair after prolonged fevers, such as typhoid, and as they do, likewise recognizes a toxic origin.

**Brown Pigmentation of the Skin,** which may sometimes take the bronzing tint seen in Addison's disease, is not so seldom observed in Graves's disease. It may involve the entire body, but is more marked in the exposed regions, such as the face, the neck, the thorax and arms. Sometimes, instead of being diffusely distributed, it is localized in patches, and in that case is more marked in the bend of the elbows, of the wrist, knees, etc. When present, it is always more marked and appears first around the eyelids, as has been shown in the chapter on Ocular Symptoms.

Circumscribed edema is sometimes observed; its site of predilection is in the eyelids; this edema sometimes has a very transient character. It is, too, of nervous origin.



## CHAPTER XXXI.

### BLOOD CHANGES IN BASEDOW'S DISEASE.

ALTHOUGH Miscowicz and Ciuffini, in 1904, found a lymphocytosis in the blood of Basedow patients, and Caro, in 1907, reported similar findings in one case, it was Kocher, however, who, in 1908, gave these findings their true significance, and considered them as the result of the disease. Since then a number of authors have published the results of their investigations upholding these conclusions. Important information can be found by the methodical examination of the blood in Graves's disease. These examinations should always be made with the patient's stomach empty in order to avoid the alimentary leukocytosis. The best time is in the morning before breakfast. The chief characteristics of the blood in Graves's disease are *leukopenia*, *hyperlymphocytosis* and *hypopolynucleosis*.

We consider as normal, blood which contains about 5,000,000 red corpuscles for men and about 4,500,000 for women; 7000 to 8000 leukocytes; 70 to 75 per cent polynuclears; 20 to 25 per cent small and large lymphocytes; 3 to 5 per cent mononuclears; 1 to 3 per cent eosinophiles; and 0.5 per cent mast cells. We shall consequently speak of leukocytosis when the number of leukocytes goes above 8000, and of leukopenia when the number goes below 7000; of hyperpolynucleosis when the number of polynuclears goes above 75 per cent, and of hypopolynucleosis when the number goes below 75 per cent; of hyperlymphocytosis when the number of lymphocytes goes above 25 per cent, and of hypolymphocytosis when this number goes below 20 per cent.

This being agreed upon, let us see what are the characteristic changes found in the blood of Graves's patients:

The number of *red blood cells* is usually normal. Not infrequently, especially in young women, this number is higher than normal, running between 5,000,000 and 6,000,000 per cubic centimeter. The hemoglobin content is usually normal. There may, however, be a slight degree of anemia in advanced cases of thyrotoxicosis. The anemia seems not to be dependent upon the thyrotoxicosis itself, but must be regarded as a secondary complication due to the disturbed nutrition.

The most important changes in the blood formula are found in the number and relative proportion of the white cells. As said before, the total number of leukocytes, as a rule, is diminished; *leukopenia* is

present. The lowest rate I have found was 3000; Kocher found it as low as 2000; at the same time the number of lymphocytes and mononuclears is increased materially. We have, consequently, a *hyperlymphocytosis*: the highest rate I have found was 75 per cent. On the other hand, the polynuclears are always found diminished in a more or less degree; their lowest rate seen was 28 per cent; we have, consequently, a *hypopolynucleosis*. It is apparent that the increase in the number of lymphocytes takes place at the cost of the number of polynuclears. If divergences are still found among authors concerning these blood findings, it is due principally to the fact that it is not yet clear to everybody how to classify the mononuclears which in certain cases show great variations. The eosinophiles are sometimes found increased in Basedow's disease, but this is not a constant finding, and has no special clinical diagnostic value. Mast cells and transitional forms are not materially affected. The behavior of the *platelets* in thyrotoxicosis is a chapter which still remains to be investigated.

In the *fruste forms* of thyrotoxicosis, the same changes appear, but on a smaller scale. In *simple goiter* unaccompanied by hyper- or hypothyroidism symptoms, the blood formula remains normal.

These laboratory findings are of good diagnostic and prognostic value. In doubtful cases where the diagnosis of thyrotoxicosis is not yet certain, a slight degree of leukopenia, of hyperlymphocytosis, and of hypopolynucleosis, will be of great help in deciding whether we have to deal with a thyrotoxic condition or not; the same is true for the prognosis. A marked leukopenia, a high lymphocytosis, a marked hypopolynucleosis, will show that the case is a serious one. A high percentage of lymphocytes without, or with only a moderate, leukopenia is of good prognostic value, whereas a marked leukopenia with a low percentage of lymphocytes must be regarded as of bad prognosis. Hyperlymphocytosis seems to be more or less dependent upon the severity of the disease, being moderate in the early stage, increasing with the intensity of the thyrotoxicosis, and diminishing gradually when the condition is getting better. The change in the blood may be followed beautifully in operative cases. The same day of the operation the lymphocytes diminish materially while the polynuclears increase; on the following days, however, the blood formula returns to its previous normal pathological condition, and only then improves gradually in direct proportion with the disease and usually becomes normal in the fully cured cases. If, in the apparently cured cases, the blood formula still remains abnormal, it is either because there is still some degree of thyrotoxicosis, or because the hyperthyroidism is gradually passing into one of hypothyroidism. Coagulability of the blood will then be the decisive argument which will tell which one of the two conditions we have to

deal with. The return to normal of the blood formula is one of the best signs of cure.

This picture of the blood in Basedow's disease, according to Kocher, is the direct result of thyrotoxicosis, either because the thyroid throws directly into the blood stream an increased number of lymphocytes, or because the thyroid secretion stimulates the function of the lymphatic system. These views seem to be upheld by Potrowsky, who found that after total removal of the thyroid in dogs, the small lymphocytes entirely disappeared from the blood. These views are corroborated, too, by the fact that thyroid feeding and the intravenous injection of thyroid extract are always accompanied by a hyperlymphocytosis and a hypopolynucleosis; finally, the changes in the blood formula and its return to normal after operation, are the strongest indication that Basedow's formula is dependent upon the thyroid pathology. Were this all, everything so far would be perfect in all these explanations. But we must not overlook the fact that we find the same blood changes in thyroid insufficiency. There the thyrotoxicosis can no longer be incriminated. What is the explanation? *Nescio*.

Lately some authors are inclined to believe that hyperlymphocytosis, hypopolynucleosis and leukopenia are not altogether dependent upon the thyroid changes, but may be the result of alterations of the *thymus*. Klose maintains that these blood changes are due altogether to thymic hyperplasia. Against such views I could cite 2 of my fatal cases, in which the blood formula was normal, although both patients had very great thymic hyperplasia, as was shown by postmortem. It is true that these 2 cases were not suffering from thyrotoxicosis but only from the mechanical symptoms caused by the large goiter. As we know that in patients with simple colloid or cystic goiters, unaccompanied by thyrotoxic symptoms, the blood formula remains normal, possibly, the same might be true for thymic hyperplasia. We may have cases in which thymic hyperplasia causes only mechanical disturbances, and other cases in which it causes thymotoxic disturbances; these cases only would then show changes in the blood formula. These views will have to be corroborated by further researches. One fact, however, is certain: the changes in the blood formula do not always go hand in hand with the amelioration of the disease. There are thyrotoxic cases which can be considered as clinically cured, and which still show even years after, the characteristic changes of the blood picture. Hence the conclusion of a number of authors that these changes in the blood are dependent upon thymic hyperplasia. Furthermore, as in myxedema, the blood picture is similar to the one seen in hyperthyroidism, and since in myxedema the thymus is nearly always hyperplastic, Klose considers this

as another proof that the blood changes are due to thymic hyperplasia, and that they are not caused by the thyroid pathology.

In conclusion we may say that the question is still an open one. It would be a mistake to think that lymphocytosis is pathognomonic for a thyroid or thymic condition only. Lymphocytosis has been found a number of times in connection with diseases of other glandular organs, such as the liver, kidneys, pancreas, parotids, etc., consequently, before giving any diagnostic value to lymphocytosis, we should carefully eliminate all other possibilities which might cause that condition. On the other hand, the absence of lymphocytosis does not necessarily mean that we must exclude thyrotoxicosis, because sometimes changes in the blood formula do not occur even in typical thyrotoxic cases. Although exceedingly important, and almost pathognomonic, these blood changes must be, however, carefully interpreted and their true origin and real value established in every given case.

Anyone who has had a great deal to do with Graves's disease must have encountered once in a while a more or less severe case in which an intercurrent disease of moderate severity has, however, proved fatal to the patient. Not very long ago I saw a case in which a moderate degree of tonsillitis terminated fatally without there being any apparent cause or complication to explain such a death. The reason must be found, very likely, in the diminished number of polynuclears. We know that these polynuclears are the defenders upon which our organism counts when it is invaded by infectious agents. They respond at once by millions to the call; they contain antitoxic, peptic and oxydative ferments, and have marked chemotactic properties. In Graves's disease the polynuclears being greatly diminished in number, and possibly inhibited by the thyrotoxin, the means of defence of the organism are reduced. This will explain why thyrotoxic patients are so vulnerable to acute infections, which in ordinary conditions would be warded off easily. It is true that in the majority of such thyrotoxic conditions, whenever an acute infection takes place, the number of lymphocytes diminishes in order to allow the polynuclears to increase. As soon, however, as the acute process is past, the blood formula returns to its previous conditions, namely, hyperlymphocytosis takes the upper hand, and the polynuclears again become reduced in number. In a few cases, however, leukocytosis and hyperpolynucleosis do not take place, or occur in such a small degree that the organism is unable successfully to meet the invaders; it offers to them no, or very little resistance; the battle is really lost before being fought.

#### **Depressor Substances in the Blood Serum of Thyrotoxic Patients.**

—In 1911, Gley announced that the serum of certain thyrotoxic patients contains a marked cardiac depressor action. He showed, too, that at



first, injection of potent thyrotoxic serum conferred a tolerance of such nature that subsequent injections of the same serum during the same experiment produced little or no effect.

In 1913, Blackford and Sanford repeated the experiment and came to the following conclusions:

"Fresh extracts made from exophthalmic thyroids contain a powerful depressor substance.

"A powerful depressor substance likewise exists in the sera obtained from certain cases of exophthalmic goiter.

"The latter substance is present in direct proportion to the clinical acuteness and severity of the disease.

"The sera from patients with non-hyperplastic thyroids do not have a depressor action."

"After an active depressor dose of the serum from a case of exophthalmic goiter, the depressor action of the extract of an exophthalmic goiter is weakened or abolished. The converse is also true. In other words, a crossed tolerance seems to exist between the depressor action of extract of exophthalmic goiter and of exophthalmic serum. It seems probable, therefore, that the depressor agent in the extract of exophthalmic thyroid and that in the serum from a case of exophthalmic goiter are of the same nature."

"No attempt has yet been made to identify the chemical nature of the depressor substances in these extracts of thyroids or of those in sera of patients affected with exophthalmic goiter. From certain experimental evidence it seems that the substance is neither cholin nor ordinary peptone."

**Coagulability of the Blood.**—Kottmann, Lidsky and Kostlivy found that in Graves's disease the blood shows a diminished coagulability, whereas, in hypothyroidism the power of coagulation of the blood is materially increased. This fact will perhaps explain why operations for Graves's disease are more bloody than those for simple goiter. This difference in the coagulating power of the blood was first attributed by Kottmann to the fact that blood in hypothyroidism contains a diminished amount of antithrombin, hence its increased coagulability, whereas in Basedow the antithrombin content is increased, hence its diminished coagulability. According to Doyon, antithrombin is given off by the liver. Kottmann claims that in Basedow's disease the viscosity of the blood is increased. This difference in the coagulability of the blood in hyperthyroidism and hypothyroidism, according to Kocher, is a constant one, and an excellent differential diagnostic symptom which should be resorted to in the doubtful cases. Indeed, since the blood changes which used to be considered as pathognomonic for Graves's disease, such as leukopenia, hyperlymphocytosis, hypopolynucleosis, are equally found in hypo-

thyroidism, the changes in the blood formula lose their diagnostic value. In doubtful cases only the coagulability of the blood will be the deciding element. It must be said, however, that Julius Bauer, who repeated Kottmann's experiments, did not obtain the same results.

Viewed from the colloidal chemistry standpoint, the reason for this perturbed coagulability of the blood is most likely due to a disturbed condition in the colloidal dispersion of fibrinogen. We know that in the ordinary conditions the fibrinogen which is present in the serum as a hydrosol, therefore called fibrinogensol, is converted into fibrinogengel. In thyrotoxicosis, the conversion of fibrinogensol into fibrinogengel is retarded or suppressed. In simple goiter it is rather accelerated, just as the thyrotoxic serum retards or suppresses the photo-chemical reaction of iod-silver, while the reaction is present or even accelerated in simple goiter.

**Adrenalinemia.**—It is more or less universally conceded today that the suprarenal bodies produce epinephrin, and that this adrenalin reaches the blood and is used to maintain the tonicity of the vascular system. Experimentally it has been found that the blood coming from the suprarenal veins contains epinephrin, and the conclusion has been drawn that the blood contains more or less adrenalin, and that this substance varies with the pathological condition.

Epinephrin has strong mydriatic properties and very likely exerts its action by influencing directly the muscular cells of the dilator muscles of the iris, and possibly by direct action upon the sympathetic nerve. The action of the epinephrin may be considered as analogous to the electrical excitation of the sympathetic nerve. Adrenalin mydriasis is found in all the conditions in which the sympathetic system is excited. It is found further in pathological conditions of the pancreas, hyperthyroidism, diabetes mellitus; it is furthermore found in many pathological conditions of the stomach, intestines, in lesions of the central nervous system and of the meningeal membranes. In such conditions mydriasis is very likely due to an irritation of the sympathetic system by the pathological condition.

The methods of determining the adrenalin content of the blood are numerous, but none are so very reliable. The test method which I have adopted is the Ehrmann method. This method consists in enucleating the eye of a frog, if possible, the *rana esculenta*, and plunging this eye into the blood serum of the patient. The time which elapses from the moment in which the eye has been put into the serum to the moment when the pupil reaches the maximal dilatation is carefully noted, and as a scale has been previously made of different solutions of epinephrin showing the length of time it takes a given solution of epinephrin to

dilate the pupil to its maximum, it is therefore easy to find out the quantity of epinephrin contained in the blood serum. This method, of course, is not an accurate one. Another objection which may be raised is that it is not at all certain that the dilatation of the pupil is due to the epinephrin; it may be due to the other sympatheticotonic substances which belong to the same class as adrenalin, such as the pituitary and thymus extracts, and which, according to Biedl, Zandler and Ranze, give also the Meltzer-Ehrmann reaction. It was, however, the best method I had at my disposal at the time. From investigations made in a great many cases with the method, I am unable to draw any practical information, because in many of the severe cases of Graves's disease, the epinephrin content of the blood was increased, but in other cases just as severe, it was only light or negative. It has been asserted that hyperlymphocytosis combined with absence of epinephrin in the blood is of bad prognosis. In my own experience I have been unable to convince myself that this is true.

**Hyperglycemia.**—Tachaus has shown that the blood of normal individuals contains an average of 0.086 per cent of sugar. If these normal individuals are fed with 100 grams of sugar, no increase in the sugar content of the blood takes place. In Basedow patients, on the contrary, as soon as they are fed with sugar, the sugar content of the blood increases to double or more of its normal rate.

This condition was termed by von Noorden *thyroid diabetes*. Jacobsen in 1913, Williams and Humphrey, in 1916, showed that injection of considerable amounts of glucose is followed by temporary hyperglycemia. It is generally accepted that when in the course of this hyperglycemia the concentration of blood sugar rises to 185 mg. per 100 cc of blood, sugar usually appears in the urine. McCasky, in 1919, who investigated this phase of metabolism in some 30 cases of exophthalmic goiter, was unable to demonstrate a specimen of sugar tolerance in the blood during the disease, although in common with others, he noted that there was a hyperglycemia even before the administration of glucose. Janney and Isaacson found that complete extirpation of the thyroid in dogs was followed by absence of hyperglycemia when large amounts of glucose were administered.

Achard, Ribot and Binet, in 1919, produced hyperglycemia in dogs by the intravenous injection of glucose. The rate and duration of the hyperglycemia depend upon the quantity of glucose injected. If adrenalin is added to the glucose the amount of hyperglycemia is considerably increased and its duration prolonged. The same is true if hypophysis extract is added to the glucose, with the difference, however, that the hyperglycemia is not as marked as in the case of adrenalin and glucose.

Extract of fresh pancreas added to the glucose injected caused a diminished hyperglycemia both in amount and duration. When added to the glucose-adrenalin mixture, pancreatic extract inhibits the action of adrenalin and of the hypophysis extract.

This hyperglycemia is consequently not a primary one but must be regarded as an alimentary hyperglycemia; it is very likely of thyroid origin, as it can be produced more or less at will by ingestion of thyroid extract. It gradually diminishes as the thyrotoxic condition improves. Flesch claims that there is an antagonism between hyperglycemia and lymphocytosis: the stronger the hyperglycemia the less the lymphocytosis, and *vice versa*.

Janney, in 1917, considered hyperglycemia response to ingested sugar to be a better test of sugar tolerance than the appearance of sugar in the urine. The sugar content in the blood was best determined in a patient who had fasted overnight and then, two hours after the ingestion, the sugar content was again determined. A patient who has fasted overnight has demonstrated pure glucose in the ratio of 1.75 gm. per kg. of body weight in a 40 per cent aqueous solution with the addition of lemon. In normal individuals there is a hyperglycemia two hours after. A normal blood-sugar curve accompanied by glycosuria usually indicates renal diabetes. All cases of Graves's disease examined show a delayed blood-sugar curve.

**Antitrypsin Content of the Blood.**—Walli found that antitrypsin in the blood of normal individuals is very rarely present. In Basedow patients, however, it seems to be constant. The clinical picture of hyperthyroidism need not be fully developed in order to have a positive finding of antitrypsin, since the reaction is present in the early incipient cases. The antitrypsin content is in direct relation to the gravity of the disease. If this test should prove correct, it would be of excellent diagnostic value when the diagnosis is doubtful.

**Complement-fixation.**—Papazoula has shown that the blood serum of Basedow patients was able to fixate the complement when mixed with antigen extracted from thyrotoxic goiters. According to this author the thyroid gland in that case acts as an antigen, thus causing the formation of antibodies. Hence the conclusion that in Graves's disease the thyroid secretion is not only quantitatively but also qualitatively affected, which is an argument in favor of dysthyroidism.

**Kottmann's Reaction.**—To understand this reaction one must have some knowledge of the fundamentals of colloid chemistry.

The latest colloid chemistry teaches that the majority of colloids present in the serum of animals are found in certain "dispersion's conditions"; this means that the colloids are contained in the fluids in a more



or less fine division of their particles. Consequently, we shall have various degrees of dispersion as follows:

Simple solution $\begin{smallmatrix} \leftarrow \\ \rightarrow \end{smallmatrix}$	Sol $\begin{smallmatrix} \leftarrow \\ \rightarrow \end{smallmatrix}$ Gel $\begin{smallmatrix} \leftarrow \\ \rightarrow \end{smallmatrix}$	Emulsion $\begin{smallmatrix} \leftarrow \\ \rightarrow \end{smallmatrix}$ Suspension
Dispersids.	Dispersoids.	Dispersion.
The colloid particles have an average diameter below $1\ \mu\mu$ .	The colloid particles have an average diameter below $1-100\ \mu\mu$	The colloid particles have an average diameter below $100\ \mu\mu$

Transitional stages are found in both directions, therefore, the arrows in both directions.

*Sol* is the abbreviated term for solution.

*Gel* is the abbreviated term for gelatine.

We speak of a *silversol*, of a *silvergel*, of an aluminiumsol, of an aluminiumgel, according to the degree of concentration and physical state of the colloid contained, the degree of dispersion remaining, however, within the limits ascribed to the dispersids and dispersoids.

Furthermore, in *suspensions* the colloid particles are more solidly linked together, while in emulsions they are in a more fluid state.

In a general way we may say that all these stages of dispersion (in which the colloid is known as *dispersum* and the diluting medium as *dispergens*) are characterized by a more or less marked degree of division of the particles. What is of importance is the physical condition of the colloids and not their chemical properties. For instance, sodium chloride may be obtained not only in its crystalloid, but also in a colloid form, just as the soaps are colloids when dissolved in water and crystalloids when dissolved in alcohol.

We come consequently to that seemingly paradoxical conclusion that there are no colloids but only colloid states.

*Technic.*—In 1920, Kottmann advised the following technic: The reaction is based upon a principle well known in photography. The photographic medium is composed of a mixture of a solution of silver nitrate, bromo-ammonium and gelatine. When the reaction takes place, resulting finally in the formation of bromosilver, the latter is found not as a bromosilversol but in so fine a state of colloid division that the gelatine-bromosilver mass becomes only of a light opalescing color. In a fresh state this mass reacts only lightly to light, but its sensibility to light can be greatly increased by heat.

In a dark room for each 1 cc of blood serum 0.25 cc of a 0.5 per cent solution of KI., and 0.3 cc of a 0.5 per cent solution of silver nitrate are added. As the silver iodide is poorly soluble in water, the serum remains practically clear, or at least is very little clouded.

The mixture is then exposed to light. Fifteen minutes' exposure before a 500 candle power electric light at a distance of 25 cm. is made. When that is done a 0.25 per cent solution of hydrochinon is added; this is done in a dark room, with red light.

A brown up to a dark coloration occurs. The intensity of the coloration serves as an index of the intensity of the reaction.

The photo-chemical reaction of the iod-silver seems to be dependent upon its state of dispersion in the serum and upon the colloidal constitution of that serum. It varies greatly with the intensity of light. Thus, the same serum when preserved for a time, and especially if exposed to the rays of the sun, will give an entirely different reaction than when examined in its fresh state, showing that colloid solutions are very labile and that their state of dispersion depends much upon time and light influences.

The practical conclusion to be drawn from the foregoing is that blood must be taken from patients on an empty stomach and that it must be examined at once. The chemical solutions used must be made fresh before using them, and the chemicals must be weighed exactly.

The process of chemical reduction can be divided into two phases:

- (1) The photochemical reduction of silver iodide to silver sub-iodide.
- (2) The conversion of the silver sub-iodide into metallic silver through the influence of hydrochinon.

It has long been known among photographers that certain substances can accentuate or retard the reaction at will. Bromide is one of them; it suppresses the photochemical reaction. Kottmann found that small doses of bromide given to a patient previously will prevent the photochemical reaction of the serum from taking place.

Kottmann observed that the reduction of silver iodide is considerably retarded in serum of thyrotoxic patients when compared with the reduction observed in the serum of simple goiter patients and of normal individuals. The difference in results is due to the exaggerated condition of dispersion of the silver iodide in the blood serum of thyrotoxic patients. This means that the colloidal chemistry of the thyrotoxic serum is so disturbed that its dispersion capacity for silver iodide is enormously increased; its reduction for the same silver iodide capacity becoming thus proportionately diminished.

Kottmann found that treatment with iodides causes the same increased conditions of dispersion of the silver iodide as observed in thyrotoxic serum and that administration of calcium preparation diminishes the dispersion power of the serum. So does sodium phosphate.

Personally, I have had no experience with the Kottmann reaction. In its author's experience it is quite reliable. How much it will be of value in the diagnosis of borderline cases remains to be seen. At any rate it is a wonderful step in the right direction.

## CHAPTER XXXII.

### DISTURBANCES IN METABOLISM.

**Basal Metabolism.**—As Benedict says:

“So truly is the heat output determined by the intensity of the vital processes that conversely, it may be stated that the level of vital activity may be inferred from the amount of heat produced.”

“While heat is the end-result of glandular and muscular activity, oxidative processes are essential factors in these transformations. Thus, the intake of oxygen is essential to combustion while the production of carbon dioxide makes up a very large part of the total oxidative activities of the body. Therefore, if one can measure accurately the carbon dioxide production, or still better the oxygen consumption, a very close estimate of the total heat production, and consequently one of the end-results of the glandular and muscular activity, may be secured.”

Clinically, one can accurately determine, by suitable measures, the basal metabolism of the patient. The term, basal metabolism, is applied to the minimal heat production in an individual after ten to eighteen hours' fasting and with the body at complete muscular rest. The method of indirect calorimetry is the one generally used for clinical purposes. This is done by determining the oxygen consumed and the  $\text{CO}_2$  excreted in a given period and by expressing the result in calories per square meter of body surface per hour. This result is called the *basal metabolic rate*. A certain norm is given for stature, weight, age and sex of the patient, and from this standard we may express plus or minus rate for the individual case. In Graves's disease the rate is definitely increased from 30 to 100 per cent. Following ligations of thyroid arteries, roentgen-ray treatments, and thyroidectomies, the basal rate shows a marked decline, the greatest, of course, subsequent to radical operations. As a valuable adjunct in the diagnosis of thyroid disorders, either hypo- or hyper-functioning, there can be no doubt that the determination of the basal metabolic rate is distinctly useful.

It was Lavoisier, in 1720, who first recognized the need of the body for oxygen, but it was not until 1850 that Regnault and Riset devised an apparatus to measure the amount of oxygen absorbed and the amount of  $\text{CO}_2$  produced. In 1894, a grant from the U. S. Government enabled Prof. Atwater, of Wesleyan University, to make further studies, but unusual impetus was given to the study by the erection of the Carnegie

Nutrition Laboratory of Boston, which was placed in charge of Prof. F. G. Benedict. In this laboratory excellent work has been carried out on both normal and pathological cases and an apparatus perfected for practical clinical use.

Lusk and Dubois have shown the close relation between direct and indirect calorimetry in determining the basal metabolic rate for clinical purposes and to indicate this several kinds of apparatus are now in use.

*Relationship between Pulse-rate and Basal Metabolism.*—Sturgis and Tompkins have shown that there is a definite relationship between the pulse-rate and the basal metabolism. For example, a pulse-rate above 90 gave a distinct rise in metabolic rate, while the cases below 90 practically all showed a normal basal metabolism. In few instances, especially those with auricular fibrillation, the pulse was distinctly slow with an increased metabolic rate. These workers conclude that a pulse-rate, in most cases at least, is an indicator of the rate of metabolism. McCaskey, with a view to determine the correlation between hyperglycemia and basal metabolism, has shown that cases with an increase of 0.1 per cent of dextrose in the blood following 100 grams of glucose on a fasting stomach means hyperglycemia, and that in practically all instances the metabolic rate was accordingly increased in proportion to the amount of blood sugar.

*Normal Standards.*—In general, the number of calories per square meter of body surface per hour for women between twenty and forty years of age is 36.9 and for men of the same age, 39.2. The variations as to age, sex, height and weight, have been made the subject of an exhaustive study by Harris and Benedict. They give the formulæ for determining the exact rate accurately for each individual. To facilitate the determinations there are in this monograph tables made up from the formulæ. On the basis of these formulæ, there is a variation of 4 to 6 per cent over the height and weight calculations of Dubois. In our own calculations we have been using the tables of Harris and Benedict.

Our procedure in determining the metabolic rate is to have the patient in bed, without food, for sixteen to eighteen hours before the test. He is brought to the laboratory in a wheel bed or chair made into a bed. We wait twenty to thirty minutes after his arrival and explain just what we expect to do so as to eliminate all disquieting factors. This preliminary procedure we consider very important, inasmuch as we have taken a rate on a highly excitable patient as plus 100 per cent above normal while the next morning it was plus 35 per cent above normal. This possible variation adds a serious source of error which must be eliminated hence we check this test by another the following day. The findings in thyrotoxicosis vary in mild cases, but are usually 20 to 30 per cent above normal standard; in moderate cases, 30 to 60 per cent above normal, and in



severe cases above 60 per cent; while occasional frank cases of exophthalmic goiter, shown to be so clinically before operation and pathologically after operation, have a normal metabolic rate, or at least within the generally accepted 10 to 15 above to 10 to 15 below normal.

In hypothyroid states this procedure is especially valuable. One can accurately measure the degree of improvement under thyroid extract or thyroxin and determine the dosage to keep the patient at the normal level.

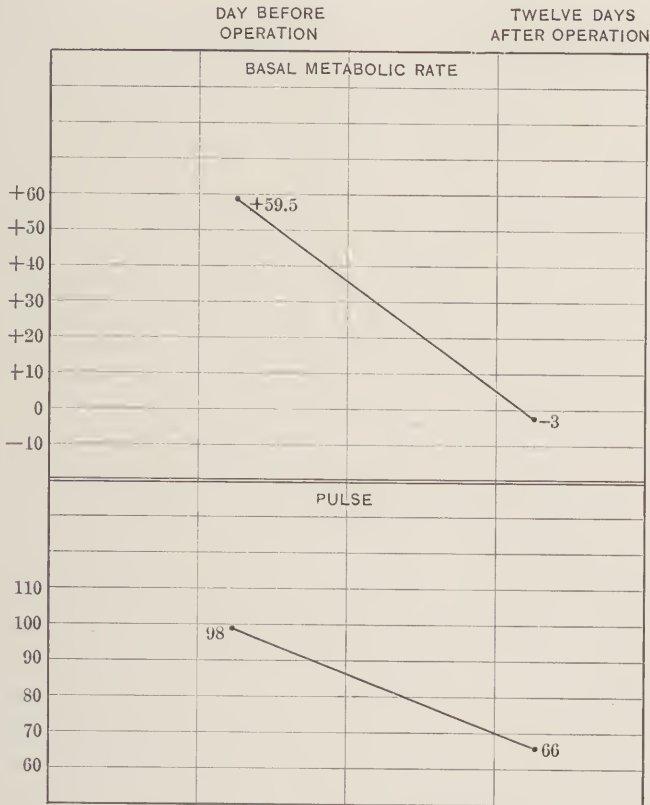


FIG. 76.—Chart showing basal metabolic rate before and after operation.

Plummer has shown that “the basal metabolism of a thyroidless individual is from 30 to 40 per cent below the average normal. The edema of myxedema develops, or at least becomes recognizable, when the basal metabolism drops from 15 to 17 per cent below the average normal. In a myxedematous person having a basal metabolism ranging near this point, the edema may appear after stress and disappear after rest. Sustained stress exhausts the thyroxin more rapidly than it can be produced by the thyroid and the basal metabolism drops a few points. A recognizable edema may disappear and reappear with a shift of 1 mg. or less

of thyroxin in the tissues of the body. A drop in the basal metabolism to 40 per cent below normal does not cause edema in the classifiable and unclassifiable conditions not due primarily to hypothyroidism. This relation of edema to the basal metabolism is of the highest significance in the differential diagnosis of primary hypothyroidism and of the other conditions with which a low metabolism is associated."

CONCLUSIONS.—The determinations of the basal metabolic rate must be added to our armamentarium as a valuable aid especially in thyrotoxic disorders, but there are many sources of error in determination no matter what form of apparatus is used, and because, as Benedict states, "There is no inflexible standard of normal metabolism for any given age, height, weight, or sex, from which the individual never varies; one must use the test as an adjunct and not as an absolute measure of the diagnostic procedure."

We have seen many cases of thyrotoxic goiter, whose thyroids have been definitely pathological and in which the clinical condition has been markedly improved by a partial thyroidectomy, but having a normal basal metabolism. On the other hand we have seen, too, cases, clinically markedly thyrotoxic, yet, the basal metabolism was normal and, again we have seen cases clinically apparently little or not at all thyrotoxic but with an unusually high basal metabolism.

In the great majority of cases the adrenalin test and the metabolic rate go hand in hand. Not always, however, by any means. In a given case, one test may be very positive while the other is practically negative.

If it is true that basal metabolism is of little value in the diagnosis of the borderline cases, it becomes, however, a very valuable aid in judging of the safety of an operation in a given thyrotoxic case where basal metabolism is very high. For instance, a basal metabolism of 50+ suggests caution, and most likely ligations had better be resorted to, instead of a resection. On the other hand a patient with a metabolic rate of 65+ who is recovering from a recent exacerbation is a safer surgical risk than the patient with a metabolic rate of 45+, who is now on the rising wave of the exacerbation.

**Loss of Flesh.**—Loss of flesh is one of the most constant and most important symptoms in Graves's disease. It goes hand in hand with muscular weakness. This loss of flesh may be either a very rapid or a very gradual one, and it is, as a rule, one of the earliest symptoms of the disease. If gastro-intestinal disturbances such as vomiting, diarrhea, etc., are present, the loss of flesh will of course be far more pronounced, but in a number of conditions there is no apparent cause for this loss of flesh. It may even occur despite a good appetite and a very liberal diet.

Fr. Müller has shown that this loss of flesh is due to the fact that the

*nitrogen* losses are increased far above the normal. Not only the metabolism of albumin is increased, but the consumption of *fat* and *carbohydrates* is also considerably exaggerated. Steyrer proved that in Graves's disease there is an increased production of calories due to the metabolism of *albumin* and *fat*. This hyperproduction of calories is independent of diet, since it occurs even when the patient remains fasting; spells of nervousness, however, increase it very materially. Magnus-Levy has shown that in Graves's disease the *gaseous exchanges* are increased, namely, that  $\text{CO}_2$  *excretion* is materially increased. While the quantity of *sodium chloride* remains about normal, the amount of *phosphates* existing in the urine of Basedow patients is greatly increased.

We may say that in Graves's disease the metabolism is profoundly disturbed, and that the various oxydating processes are constantly and always materially increased. The patient is "burning the candle at both ends." He keeps up the fire by consuming the albumin, fats and carbohydrates of the body. If the patient is able to offset the losses by a good diet, all well and good: the equilibrium between the intake and exchanges will remain more or less undisturbed; if not, loss of flesh will follow. If loss of flesh nevertheless occurs despite a free diet, it will be due to an impaired resorption and assimilation of the gastro-intestinal tract. This increase in all the oxydating processes is most likely of toxic origin, either because it stimulates the centers of heat, or because it influences the nervous system controlling metabolism.

**Temperature.**—With the increase of all the oxydating processes, we might then expect an increase of the bodily temperature. And so it happens. Rise in temperature is frequently seen in Basedow patients. It is most inconstant and most irregular; it goes and comes, may last over a few days and then become normal again. There seems to be no apparent cause for this. Temperature, however, seems to follow the periods of exacerbation of the disease. It is, as a rule, not high, hovering around 100, seldom goes above 101, and does so only when the case is a very severe one. Although the increase in the oxydating processes may be fully incriminated, this rise in temperature is most likely due to some thyrotoxic influence upon the nervous centers regulating the bodily temperature.

**The Goetsch or Adrenalin Test.**—Applying the adrenalin test advocated by Eppinger and Hesse in their study of sympatheticotonia, Goetsch proposed the following method for determining the degree of thyrotoxicosis in cases that may show only a few or no symptoms:

"Two readings are taken at five-minute intervals of the blood-pressure, systolic and diastolic, pulse-rate and respiration. A note is made of the subjective and objective condition of the patient. This includes the state of the subjective nervous manifestations, the throbbing,

heat and cold sensations, asthenia, and the objective signs, such as pallor or flushing of the hands and face, the size of the pupils, throbbing of the neck vessels and precordium, tremor, temperature of the hands and feet, perspiration, and any other characteristic signs or symptoms noted. These signs are all noted previously to the injection of the adrenalin so that comparison may be made after the injection.

"A hypodermic syringe armed with a fine needle, which, when injected causes little discomfort, is then used to inject 0.5 cc (7.5 minims) of the commercial 1 to 1000 solution of adrenalin chloride (Parke, Davis & Co.) into the deltoid region subcutaneously. Intramuscular and intravenous injections are not given. Readings are then made every two and one-half minutes for ten minutes, then every five minutes up to one hour, and then every ten minutes for half an hour or longer. At the end of one and one-half hours the reaction has usually entirely passed off, sometimes earlier. The repeated early readings are made in order not to miss certain reactions on the part of the pulse and blood-pressure that may come on in less than five minutes after the injection is made. This is particularly true of cases of active hyperthyroidism.

"In a positive reaction there is usually an early rise in blood-pressure, in pulse, of over ten points at least; there may be a rise of as much as fifty points or even more. In the course of thirty to thirty-five minutes there is a moderate fall, then a second slight secondary rise, then a second fall to the normal in about one and one-half hours. Along with these, one sees an exaggeration of the clinical picture of hyperthyroidism brought out, especially the nervous manifestations. The particular symptoms of which the patient complains are usually increased, and in addition there are brought out many symptoms which have been latent. Thus, it is not uncommon to have extrasystoles brought out after injection of adrenalin. The patient is usually aware of them and may tell one that she has felt the same thing a year or two previously, at which time the symptoms of the disease were more active.

"The following may all or in part be found: increased tremor, apprehensions, throbbing, asthenia, and in fact an increase of any of the symptoms of which the patient may have complained. Vasomotor changes may be present, namely, an early pallor of the face, lips and fingers, due to vasoconstriction, to be followed in fifteen to thirty minutes by a stage of vasodilatation with flushing and sweating. There may be a slight rise of temperature and a slight diuresis.

"In order to interpret a test as positive we have regarded it as necessary to have a majority of these signs and symptoms definitely brought out or increased. Thus, there is at times a considerable increase of pulse-rate, without much increase in the systolic blood-pressure, but with a considerable increase or exacerbation of the objective signs and symp-



toms; or there may be an increase of ten points in the pulse and blood-pressure and a moderate increase of the symptoms and signs; or again, there may be only slight changes in the pulse and blood-pressure and considerable change in the signs and symptoms. These may be regarded as positive. In a word, then, one must consider the entire clinical picture produced in order to gain a correct interpretation just as in the disease itself one cannot expect every one of the characteristic signs and symptoms to be present in order to make a diagnosis."

Goetsch is very much inclined to regard the epinephrin test as almost pathognomonic for hyperthyroidism. He states that negative results exclude hyperthyroidism except in very bad cases where the patient is so weakened that the test may show positively. According to him, certain obscure cases presenting a number of thyrotoxic symptoms show a thyroid with a definite pathology which he calls "diffuse adenomatosis," and may be diagnosed by a positive epinephrin test, when other means, as for example basal metabolic rate, do not aid in diagnosis. Cannon showed that the adrenalin test is an indicator of the tonus of the sympathetic nervous system so that the positive epinephrin test means *sympatheticotonia*, which is coming back to what Eppinger and Hesse said long ago. Goetsch argues that the most frequent cause of the latter condition is hyperthyroidism.

In our own experience with the adrenalin test in several hundred cases, we have found it to be correlated with the clinical findings in most instances, but in quite a few, the basal metabolic rates were distinctly increased even as much as 33 per cent, while the adrenalin test was negative. In some frank cases of Basedow's disease the test was only moderately positive. From our own experience with the test we should consider it worthy of a place in diagnosing thyrotoxic states, but that too much reliance should not be placed upon the findings. It should be correlated with the physical findings in each case and should not be depended upon for an absolute diagnosis.

The adrenalin test is first and above all an indicator of hypersensitiveness of the sympathetic nervous system. It is not pathognomonic of thyrotoxicosis, and although in the majority of cases of such condition the test is positive, there are cases of undoubted thyrotoxic type, well marked clinically, where the reaction fails to be positive, while, on the other hand, the positive reaction is found in some apparently normal individuals in a number of neurasthenics, of psychoneurotics, of patients convalescing from acute infections. Frazier and Wilson and Peabody and Smith have obtained a positive test in men with irritable heart in whom the thyroid had not been established as the etiological factor. Finally, a positive epinephrin reaction may be associated with hyperfunction of the adrenals.

As sympatheticotonia is usually directly related to thyrotoxicosis, a positive epinephrin test acquires a good indirect diagnostic value, but as said before is not pathognomonic of thyrotoxicosis.

### GLYCOSURIA AND DIABETES IN GRAVES'S DISEASE.

As a general fact sugar may be found in the urine of any individual after a certain amount of sugar has been consumed. We know that the coefficient of absorption for sugar varies with each normal individual; as soon as this coefficient is overstepped, then sugar appears in the urine. This is what we call *alimentary glycosuria*. In *diabetes*, on the other hand, sugar is found in the urine despite the fact that sugar and carbohydrates are withheld from the patient. It is not enough, however, once in a while, to find sugar in the urine of a patient in order to diagnose diabetes, since we might erroneously consider as diabetes a transient form of alimentary glycosuria. Glycosuria must last for a long time and be independent of food, before it can be considered as true diabetes; furthermore, diabetes is, as a rule, accompanied by polyuria and thirst.

In Graves's disease *alimentary glycosuria* is far more frequent than *diabetes*: Hirschl found it in 30 per cent and Schulze in 25 per cent of their respective cases. These figures may not represent the true percentages for all cases known, but the fact remains that alimentary glycosuria is comparatively frequent in Graves's disease.

Far more frequent than the alimentary glycosuria is that one which appears after small doses of adrenalin are given to a Basedow patient who has just ingested 100 grams of sugar. According to Schulze, this alimentary glycosuria of adrenal origin appears in 80 per cent of the patients.

*True diabetes*, on the other hand, is more rare and, according to reliable statistics, is not found in more than 3 per cent of the cases. It usually occurs after Graves's disease is far advanced. The quantity of sugar found in the urine is, as a rule, moderate; in severe cases, however, it may be very large.

The presence of diabetes in Graves's disease must be always regarded as a serious complication and of bad prognosis. Ordinarily as soon as diabetes occurs, the patient begins to lose flesh and complains of an intense muscular weakness. Despite the fact that diabetes is far more frequent in men, the combination of Basedow and diabetes is more frequently seen in women.

To claim that all cases of diabetes and alimentary glycosuria complicating Graves's disease are of thyroid origin would be folly. A number

of them supervene as an independent complication and have no relation to thyrotoxicosis. This, however, is not true for all cases. A number of clinical as well as experimental observations seem to prove that there is an intimate relation between the thyroid and glycosuria. Bécclère reports the case of a male, thirty-two years old, who was suffering from myxedema. In the course of eleven days this patient absorbed 93 fresh thyroid glands of sheep; palpitation, tremor, dyspnea, profuse perspiration, insomnia and polyuria became very marked. Urine analysis showed *albumin* and *sugar*. Nothaft reports the observation of a man, forty-three years old, who in order to get thinner took a thousand tablets of thyroid extract of 5 grains each in five weeks. After three weeks the patient began to develop marked exophthalmic symptoms; the urine contained 1 per cent of sugar. F. Müller saw a patient who had a light form of Graves's disease, and who was fed with thyroid extract tablets; symptoms of hyperthyroidism became extremely marked. Severe diabetes developed and death ensued. In a myxedematous patient fed with thyroid extract, Ewald found 4 per cent of sugar. This sugar could be made to appear and disappear at will by regulating the thyroid feeding. Von Noorden reports 17 cases of obesity treated with thyroid extract; in 5 of them sugar was found during the treatment. Rohdenburg, in 1920, cites a family in which glycosuria was increased in intensity after the oral administration of either thyroid gland or adrenal. One member of this family was cured of a glycosuria after a partial thyroidectomy. In the second case, the patient, who had previously had a portion of the thyroid removed for exophthalmic goiter, developed glycosuria several years later. Glycosuria in this case also disappeared after thyroidectomy. A number of other clinical as well as experimental cases can be cited in which thyroid feeding had caused glycosuria. In the presence of all these facts it is difficult not to admit that there is a relation between the thyroid and glycosuria, and that in Graves's disease the presence of sugar in the urine must be referred to the hyperfunction of the thyroid, combined with an exaggerated excitation of the sympathetic nerve and a pancreatic insufficiency. We have then to deal with a *thyreogene glycosuria*. Thyreogene glycosuria is characterized by the fact that it develops with Graves's disease and disappears with its improvement. Thyreogene glycosuria seems to be more frequent in traumatic Basedow and is often combined with other disturbances in the resorption of fat. That the thyroid intervenes in the production of glycosuria is so much more plausible since glycosuria may be caused by other glands than the thyroid, as for instance, the hypophysis, suprarenal bodies, liver, etc.

**Polyuria.**—Polyuria is often seen in Graves's disease; it is sometimes an early symptom and occurs without any apparent pathological condition of the kidneys. It is very likely a symptom of nervous origin.

**Polydipsia.**—Knowing how much Basedow patients perspire and often suffer from diarrhea, vomiting and polyuria, in short, knowing that they are losing fluids in many ways, no one will wonder that they often complain of thirst, and that they drink water abundantly. However, the etiology of polydipsia is not quite so simple, and must be regarded, too, as a symptom of nervous origin, probably due to the irritation of some buboprotuberential centers.

**Albuminuria.**—Traces of albumin are sometimes found in Graves's disease; they are not connected, as a rule, with any disease of the kidneys, as no cylinders and no epithelial cells are present in the urine. It is most likely of toxic origin, and disappears as soon as the condition subsides.

### THYROTOXICOSIS IS A CHRONIC DISEASE.

Now that we have studied all the symptoms and followed their development, although at first the whole symptom-complex seemed stormy and erratic, we can but be impressed by this one fact, namely, that the disease is *essentially chronic*. No matter how various and changing the symptoms are, no matter if a given case apparently changes its physiognomy hundreds of times during its course, and no matter if at times some symptoms become acute and subside again, nevertheless the general tendency of the entire process is to be a chronic one. The disease follows a cycle, which grossly speaking can be said to be identical with itself. It usually begins insidiously, reaches gradually its full development, shows periods of betterment, alternating with spells of exacerbation, lasts years and then finally either takes a decisive turn for the best, or terminates by death. No matter how various its manifestations are, the main symptoms are always constant in their character. Thus tachycardia, for instance, will remain identical with itself throughout the entire course of the disease so as to resemble no other form of tachycardia. The same is true for tremor. Vomiting and diarrhea may last weeks and months, may come and go without changing in their nature, and without leading into a gastritis or an enteritis. And so on for the other symptoms.

### FULMINATING FORMS OF GRAVES'S DISEASE.

That, however, one will meet once in a while with rapidly evolving cases of Graves's disease there is no doubt: the condition begins, develops and terminates by death in a very short time, within a few weeks or months. From its inception the disease takes on a malignant form;



tachycardia and nervousness are intensely marked, and the gastro-intestinal symptoms are especially alarming; vomiting and diarrhea are continuous and become uncontrollable. The patient is profoundly thyrotoxic, and since little or no food is retained, the patient sinks rapidly, and death follows after a few weeks, with marked symptoms of acidosis. In all the fulminating forms of Graves's disease which I have seen, the gastro-intestinal symptoms were always the leading ones.

**ALL THE THYROTOXIC SYMPTOMS ARE WORSE IN THE MORNING.**

I believe anyone who has had wide experience with Graves's disease will agree with W. H. Thomson when he says, "If it be asked what are the most peculiar or most characteristic features of Graves's disease, I would answer that next to its specific tachycardia is the morning exacerbation of its symptoms." No careful observer can fail to be impressed by this singular phenomenon. I have looked for that symptom in all cases of goiter which have come under my observation, and I must say that in the great majority of cases, no matter if they were true cases of Graves's disease or simple goiters complicated with some thyrotoxic symptoms, this symptom was nearly always present. Without any hesitation the patients admitted that they were decidedly worse in the morning and would get better toward evening. When they rose they felt more tired than when they went to bed; they complained of an intense general depression; they were "good for nothing." All their thyrotoxic symptoms seemed to be more exaggerated, and tremor became more marked, so as to prevent the patient from doing any work in the morning, whereas in the afternoon such work was possible. Palpitations and nervousness became more intense but subsided toward evening. Headaches, too, were more accentuated in the morning, and the patients complained of heavy weights upon their spirits, and of a beclouding of the mind so as to preclude the possibility of mental work, or of concentration of the mind until late in the afternoon. If gastro-intestinal symptoms were present, vomiting and diarrhea underwent marked exacerbations toward morning and subsided toward evening. In short, the entire chain of thyrotoxic symptoms became aggravated in the morning. This symptom is very peculiar to, and almost characteristic of, Graves's disease. Hysteria has nothing to do with its production; it is very likely due to some disturbance in the biological chemistry of the organism, more marked at that time of the day. But what this disturbance really is and why it takes place, is still an open question.

## CHAPTER XXXIII.

### BORDERLINE OR FRUSTE FORMS OF HYPERTHYROIDISM.

It is not usual to find all the thyrotoxic symptoms ordinarily seen in Graves's disease equally developed in the same case; as a rule some of them are more prominently developed than others, while frequently, quite a few even fail to be present. In these cases, however, the diagnosis does not offer great difficulties because one or more of the cardinal symptoms will clear at once the diagnosis. Even if one's judgment has been sidetracked, as a rule, the general physiognomy of the case, its course of development and its behavior will soon betray its true nature. There are cases, however, which require a great deal of experience, sagacity and judgment before one dares to venture the diagnosis of thyrotoxicosis. There none of the cardinal symptoms are present, or at least they are so insufficiently developed that a diagnosis of thyrotoxicosis is scarcely warranted; yet, in the last analysis these cases are of thyrotoxic origin. They are incomplete forms of thyrotoxicosis; they are called *fruste*, or *borderline forms of hyperthyroidism*. They constitute what I would call *small hyperthyroidism*. As we have the great and small hypothyroidism, so we have the great and small hyperthyroidism.

These fruste cases in which the majority of the classical symptoms are absent are very apt to be overlooked, either because of lack of experience, or because these cases are so atypical that it is difficult at first to trace them back to their true origin. On the other hand, there is no doubt, however, that these fruste forms of hyperthyroidism are far more frequent than is generally suspected. If they were all recognized, it would be found that they constitute a substantial percentage of the total of patients seeking medical relief.

An incomplete form of thyrotoxicosis frequently seen is that one where the heart-rate is above normal, where the patient complains of a general throbbing of the arteries, or of palpitation. At the same time there is a marked instability of the nervous system, yet, physical examination of the nervous, cardiac, urinary and other systems fails to reveal anything pathological. No apparent cause can be found to explain that condition. Such cases are often only *fruste forms of hyperthyroidism*. If, perchance, one is able to detect some other concomitant thyrotoxic symptoms, such as possibly a small thyroid hypertrophy, some tremor, etc., then doubt is no longer permissible; this is a *fruste form of hyperthyroidism*.

There are numbers of young women who at the time of puberty complain of palpitation, tachycardia, fatigue, loss of energy and of some swelling of the feet. As a rule they are regarded as chlorotic, yet laboratory findings generally show that the blood is normal. If at the same time such patients happen to have occasional rises in temperature, and if they also complain of sweating, they are very apt to be considered as tuberculous and treated accordingly. However, should a careful examination be made, some nervousness, possibly even some psychic disturbances, might be found—all facts showing that such patients are suffering from fruste forms of hyperthyroidism secondary to the maturation of their genital systems. As soon as the genital process is settled and the organism has found its equilibrium, the thyrotoxic syndrome ordinarily subsides and then these patients again regain their health. The same is true for women *at the menopause*. They commonly complain at that time of hot flashes, palpitation, nervousness, tremor, sweating, of occasional gastro-intestinal disturbances, etc. Examination reveals a moderate degree of tachycardia, little or no apparent enlargement of the thyroid, and no ocular symptoms. Ovarian extracts remain without effect. Such cases are regarded as nervous patients, and treated with all the tonics, sedatives, cardiac stimulants, etc., imaginable. Little or no results are obtained because the real cause is to be found in the hyperfunction of the thyroid. These cases are, too, *fruste forms of hyperthyroidism*.

Not infrequently we see patients who apparently have a simple non-toxic goiter and who intermittently may complain of cardiovascular and nervous symptoms. Once in awhile they may have an occasional diarrhea alternating with constipation. This condition may go on for years, off and on, periods of complete welfare alternating with periods of thyrotoxicosis. These cases, too, are *fruste forms of hyperthyroidism*. In other cases there is apparently no thyroid enlargement. The thyrotoxic symptoms are more or less of vague nature, characterized by some nervousness, and some tremor, by periods of muscular asthenia, by occasional palpitation, and occasionally by some tachycardia especially connected with physical effort, by headaches, and at times by indigestion or hyperacidity, and by some occasional menstrual disturbances. All these symptoms experience periods of exacerbation and improvement. They come and go; the syndrome is of protean type. These patients, as a rule, do not stand easily acute infections; they do not recover as quickly as others. Any psychic shock, even of moderate degree, will leave on them traces for weeks and months, while a normal individual would not be feazed by it. Such patients are treated either for gastro-intestinal troubles, or for menstrual disturbances, or for nervousness, etc. No, or very little, improvement is gained by such

therapeutics; they may even be made worse. If, however, the correct diagnosis is made, and the case regarded as a fruste form of hyperthyroidism, and the correct treatment is instituted, these patients may be greatly benefited. Every medical means being exhausted in vain, I have operated a few of them and cured them entirely.

There are fruste forms of hyperthyroidism due to gastro-intestinal ptosis causing an auto-intoxication which in turn results in the production of a group of thyrotoxic symptoms. These symptoms may be of severe nature, and are especially characterized by nervousness, palpitation, tremor, loss of flesh, and intense asthenic symptoms. They may resist every medical treatment. One of my most grateful patients is a young woman who had a marked gastro-intestinal ptosis, causing spells of weakness, muscular asthenia, nervousness, loss of flesh, intermittent thyroid hyperplasia, palpitation and tachycardia, etc., which would incapacitate her for months at a time. A ventrofixation of the stomach and transverse colon performed some years ago cured her permanently. That, too, was a *fruste form of hyperthyroidism*, secondary to gastro-intestinal auto-intoxication.

There are fruste forms of hyperthyroidism in which besides some insignificant secondary thyrotoxic symptoms the only marking feature is possibly a glycosuria or fatty stools. As shown by Falta, such cases may be, too, *obscure forms of hyperthyroidism* because indirect intervention upon the thyroid by operation or  $x$ -rays has brought about cures.

Fruste forms of hyperthyroidism are observed, too, in conjunction with pelvic diseases. There, too, a timely operation upon the diseased pelvic organ may restore the patient to health.

In conclusion we may say that these fruste forms of hyperthyroidism may have the most protean character. In some of them we find only thyroid enlargement, in some others, tachycardia, in some others tremor, in some others the staring and glaring look, in others nervous instability, hot flashes, loss of flesh, gastro-intestinal disturbances, psychic troubles, etc. A great many of these cases are secondary to some definite pathological condition. For a great many others there seems to be no apparent cause.

I should not want to be accused of chauvinism, of seeing thyrotoxicosis everywhere. Discretion, judgment, clinical sense must be our guide. We must remember that "too little," just as well as "too much," always spoils everything, or as the French say: "*Le trop et le trop peu gâtent tous les jeux.*"

#### DIFFUSE INTERALVEOLAR ADENOMATOSIS.

Goetsch writes: "There is a group of so-called borderline cases which heretofore have been very difficult of diagnosis, and even more difficult



with reference to a satisfactory treatment. The individuals belonging to this group are of no characteristic age, but are mostly young adults. They present a syndrome characteristic of possible hyperthyroidism, incipient tuberculosis, neurocirculatory asthenia and allied conditions. They fail to show positive eye signs, or even positive clinical findings in the thyroid gland. They fail, furthermore, to respond to ordinary medical and hygienic measures. Upon further examination they are found to give a positive reaction to the epinephrin test, but on the other hand, as shown by Woodbury, in many instances they fail to show increased basal metabolism. In this type of case a rather extensive bilateral partial resection of the thyroid gland is followed by very definite and often striking improvement."

"In the gross and microscopical study of the thyroid glands from these patients I found some peculiarities which have led me to think that we are dealing with a new clinicopathological syndrome in thyroid disorders, which is a true hyperthyroidism based upon a peculiar and very interesting pathological change in the thyroid gland. This change is neither of the nature of that found in puberty hyperplasia, nor in Graves's disease, nor in exophthalmic goiter, nor is it of the type in which true discrete encapsulated nodules, the so-called 'fetal adenomata' are found. The glandular pathology in these latter types of thyroid disorder is readily recognized and is well known to be capable of producing hyperthyroidism. However, in this new and obscure group of which I am speaking, the following characteristics are fairly uniform. Upon physical examination the thyroid gland is often found moderately enlarged, but may be neither visibly nor palpably so. It is firm, and slightly granular or lobulated. No definite nodules are palpable, and signs of increased vascularity such as thrills or bruits in the gland or at the poles, are not demonstrable. At operation one characteristically finds that a peculiar periglandular fibrosis has caused the gland to become loosely, or sometimes quite firmly, adherent by its thickened capsule to the prethyroid muscles, and to the large vessels and sternocleidomastoid laterally. The appearance reminds one of a possible mild periglandular reaction, which sometimes makes difficult the delivery of the thyroid lobe. There is increased vascularity, particularly of a venous character in the capsule of the gland. The thyroid arteries are only slightly, if at all, enlarged. The gland contains a moderate amount of colloid. It is of 'rubbery' or 'spongy' consistence, friable, more than normally vascular and has a marked tendency to ooze from the cut surface. There is not the familiar increased consistence of the gland as seen in exophthalmic goiter, nor is there the glistening character seen in colloid glands.

"The microscopical findings are fairly uniform in these glands. The most characteristic feature is the readily recognizable increase in the inter-

stitial cells, the so-called fetal cells, which are themselves characterized by being without any very definite arrangement. They are large and have a fairly clear protoplasm and a round, vesicular nucleus. They can be distinguished from the lymphoid-cell accumulations, which are also common, by the fact that the latter cells are much smaller, have very little protoplasm and a dense pycnotic nucleus. This interstitial tissue is distributed throughout the gland substance and is nowhere aggregated into encapsulated nodules, as one may see in true adenoma. The granular acini are mostly small and irregular in size. One sees often numbers of very small acini in the midst of, and apparently derived from, the interstitial tissue, and appearing on cross-section like a globule of colloid surrounded by ten to twelve cells. The acinar cells themselves are usually low, thinned out, and do not of themselves appear active, nor are they as active as indicated by the presence of mitochondria, which are usually very few or practically absent. In other words, the hyperthyroidism which occurs with this change in the thyroid is not due to an increased activity of the acinar cells. In this respect the acinar cells differ from those seen either in the normal gland where they are cuboidal, or in the puberty hyperplastic gland, or in exophthalmic goiter, in which they are cuboidal to columnar and rich in protoplasm, containing abundant mitochondria. Occasionally very small young adenomata are seen no larger than a wheat grain, but this is exceptional. These very small adenomata may possibly be regarded as an index of the fact that the fetal tissue in the thyroid is stimulated to activity and overgrowth by some hidden force. There is some increase in the fibrous tissue which tends to divide the gland into small lobules, easily recognizable under the microscope. Because of the increased amount of diffuse interstitial tissue which is greater with the more toxic grades of hyperthyroidism found in these cases, and which we believe is derived from the so-called fetal cells of Wölfler because of the numerous small, apparently newly formed acini, and the increase in lymphoid cell accumulation, because of the absence of true discrete adenomata, and because finally of the hypoplasia rather than hyperplasia of the alveolar cells, I have, for want of a better term, called this condition, 'diffuse adenomatosis.' This may not be a very fortunate term, but it has the value of being descriptive. I wish to emphasize again, that the appearance of these glands is decidedly different from that seen in puberty, hypertrophy and hyperplasia, and in exophthalmic goiter, in which there is a hyperplasia of the alveolar cells and in which the interstitial tissue is almost entirely absent. Furthermore, the picture is very different from that seen in true adenoma, which occurs as an encapsulated tumor in an otherwise fairly normal-looking gland.

"The fact that this change is responsible for hyperthyroidism, to my mind, is shown by the fact that (1) there is an associated syndrome

produced, which is more or less characteristic of the hyperthyroid state; (2) there is a failure to improve under the ordinary medical and hygienic measures, which are directed to the treatment of similar nervous conditions; (3) there is a positive reaction to the epinephrin-chloride test; (4) after resection of the thyroid, there is a diminution, if not disappearance, of this hypersensitiveness with a considerable improvement, in fact, almost a cure in some cases; (5) in the gland there are found changes which are characteristic and very different from the normal appearing gland and very different also from the other well-known pathological changes in the thyroid. Should one feel that these cases are not hyperthyroid there still remains to be explained the rather typical symptomatology, the positive epinephrin-chloride test, the improvement after operation, and the very characteristic changes in the gland under microscopical examination."

In this connection it is well to remember that the thyroid cells occur as two types, the *alveolar* type forming the well-known vesicles containing more or less colloid and the *interalveolar* type, composed of more or less numerous thyroid cells, which spread among the alveoli without assuming in any way a disposition to suggest alveoli. These cells are regarded by some as fetal cells. These fetal cells, however, have nothing to do with the formation of the adenoma of Wölfler, since the staining capacities of the true Wölfler adenomatous cells and the interalveolar cells are entirely different. From the histochemical standpoint, the interalveolar cells seem to be rather of the same nature as those of the alveolar type, and consequently are most likely endowed with the same physiological properties.

Regarding the term "diffuse adenomatosis," I should think that the name "diffuse interalveolar adenomatosis," would be clearer, as we have already the "diffuse parenchymatous hyperplasia," which is in itself a diffuse adenomatosis affecting the alveolar cells instead of the interalveolar ones.

In singling out this form of adenomatosis as a pathological entity, *per se*, Goetsch has brought into the already complex problem of thyroid pathology a valuable adjunct which will enable us to be somewhat more specific in our discussions. When, however, he seeks to make this pathological phase of the thyroid suit a distinct clinical entity, I do not know how far we shall be able to follow him and to agree with him.

In my microscopical experience which, roughly speaking, is well over 2500 thyroids, many hundreds having been obtained from postmortem, I have observed this diffuse interalveolar adenomatosis in many instances. In some cases it was only moderately marked; in others the whole gland seemed to be almost wholly composed of interalveolar cells. Now, these glands came from patients who had died from the most varied diseases, and no doubt some of the patients must have offered the moderate hyper-



thyroid syndrome described by Goetsch, but many, I am sure, did not. My master, Professor Stilling, and I at the time, used to regard these glands as belonging to the fetal stage which I have described in the chapter on Embryology. We assumed that, for one reason or another, differentiation of the fetal stage into the adult or vesicular stage had not taken place.

That these diffuse interalveolar cells should, for some reason unknown to us, undergo hyperplastic and functional activity, just as the alveolar cells do, stands enough to reason, as long as we assume that both types are of the same variety. That they are very active, is well shown by Goetsch, by the fact that mitochondria is quite marked, while it is not as prominent, or may even be absent, in the alveolar cells.

Then the question arises as to just why one type is more affected than the other. This, of course, no one knows. Possibly the fact that they are more closely related to the embryonic type gives them different chemical affinities—which will react to certain chemotoxic irritations while the alveolar cells will not. One must not forget that in these cases of diffuse interalveolar adenomatosis accompanied by thyrotoxic symptoms if careful microscopical examinations are made of various parts of the gland, especially in seriated sections, one will usually find, here and there, islands of hyperplastic alveolar cells, unmistakably thyrotoxic in character.

The arguments brought forth by Goetsch to substantiate his claim that the diffuse interalveolar adenomatosis is responsible for the clinical syndrome which he describes, namely, the presence of hyperthyroid states, the failure to respond to medical treatment, the positive epinephrin test, the improvement after surgical treatment, etc., are not without recourse, inasmuch as the same conditions obtain in cases where there is no diffuse interalveolar adenomatosis.

So far as I am personally concerned, I cannot see that these borderline cases of thyrotoxicosis constitute a clinical entity *per se* different from the well-developed cases of thyrotoxicosis, no more than I can see that hyperthyroidism is a clinical entity different from exophthalmic goiter, as Plummer would have us see it. In my judgment, all such cases recognize fundamentally the same cause, namely, hyperfunction of the thyroid. They are all various degrees of thyroid intoxication on account of which in some instances, some organs or groups of organs may become more involved than in others.

My surgical experience in these so-called borderline cases has not been uniformly satisfactory. To be sure, in some instances, the results obtained were absolutely gratifying. But in some others, they were not. Most likely in these cases, the primary disturbance was not of thyroid origin. It must have centered upon some other organ (one or more) of internal secretion, or upon some focal infection, etc.



## CHAPTER XXXIV.

### HYPERTHYROIDISM AND HYPOTHYROIDISM.

IT seems at first nonsensical to claim that symptoms of thyroid insufficiency may coexist with those of Graves's disease, in short, that we may have at the same time *hypothyroidism* and *hyperthyroidism*; yet that there can be such a thing there is no doubt. The thing seems at first unacceptable because we think only of the fully developed form of hypothyroidism. We forget that until the condition has reached its full development there are numbers of intermediary stages, in short, that we have *fruste forms* of hypothyroidism as well as of hyperthyroidism. No one, I am sure, will deny that a given case of Graves's disease may ultimately turn into a myxedematous condition. We have stated more than once before that a Basedow patient, provided he lives long enough and the thyrotoxic process keeps up, is logically destined to become a myxedematous case. A number of authenticated cases could be cited to support this statement, so that there can be no doubt about it. For instance, Joffroy and Achard reported the case of a young woman, twenty-three years old, who had a typical Basedow and who finally developed a typical cachexia thyreopriva. The autopsy showed a sarcoma of the pleural cavity and a more or less complete destruction of the thyroid at which place connective tissue only was to be found.

How shall we explain the combination of these two conditions in Graves's disease? Because there the gland keeps up burning at a fast pace. This obviously cannot last forever. There comes a time when the gland is exhausted; the epithelial elements become "stale," undergo degeneration, and are gradually replaced by connective tissue, thus naturally leading into hypofunction, and consequently into hypothyroidism. Tachycardia, nervousness, tremor, loss of flesh, etc., gradually subside; and little by little the patient sees his thyrotoxic condition improve. Everybody thinks the cure is near. But, alas, this does not last long; it is only a transitory stage. The patient's spirits soon become curbed, his eyes lose their brilliancy and become dull; nervousness gradually fades away into quiet and rest; the intelligence becomes weak and lazy; tachycardia gradually subsides, and a suspicious adipose tissue of yellowish tint takes the place of the previous extreme thinness of the skin. The patient falls into a state of marasmus. He got rid of his hyperthyroidism only to fall into a state which is just as bad, hypothy-

roidism. He saved himself from Charybdis only to fall into Scylla. Until, however, hypothyroidism is fully developed, symptoms belonging to both conditions remain mixed together. Even when cachexia strumipriva is fully developed, there still remain some thyrotoxic symptoms which will show that both conditions may exist at the same time in the same patient. The case is an odd mixture of the wreckage of Graves's disease and thyroid insufficiency (Fig. 77).

As a rule the symptoms of hyperthyroidism still remain the predominant ones; only a few isolated symptoms may point toward hypothyroidism. For instance, the patient may put on an excessive amount of fat, while at the same time his skin becomes dry and scaly. In some



FIG. 77.—“Burned out” thyroid. Symptoms of hyper- and hypothyroidism combined.

other instances his mental activity becomes dull, the memory loses its reliability, the patient is quiet, the movements are slow; in short, the patient develops a new condition in direct contrast to the previous one in which he was constantly nervous and agitated. Yet the other thyrotoxic symptoms remain the same. The whole condition may show periods of improvement and exacerbation.

The reverse may be true. Some thyrotoxic symptoms may occur during the course of the cachexia strumipriva; this, however, is rare, but has been observed by men of note, as Kocher, for instance.

The possibility of the coexistence of hypothyroidism and hyperthyroidism will become more plausible and intelligible if we remember that a gland such as the thyroid has not only one function, but many of them. It contains a number of lipoids, each one of them having a definite action on the metabolism. We have already stated that Iscovesco isolated from the thyroid several lipoids, each one affected with different properties. One of them, for instance, injected into animals causes myxedema; another, exophthalmic goiter, another had a marked influence upon the ovaries, and so on. If this should be true, and should be further corroborated, the explanation for the existence of hypothyroidism and hyperthyroidism would then be a simple one. *A priori* at least, according to all that we know of the glands of internal secretion, these findings of Iscovesco's seem rational. We know that adrenalin in small doses, for instance, causes vasodilatation, and in large doses, vasoconstriction.

## CHAPTER XXXV.

### INFANTILE AND JUVENILE HYPERTHYROIDISM.

As we have an infantile, a juvenile, an adolescent and an adult hypothyroidism, so we have also an *infantile, a juvenile, an adolescent, and an adult hyperthyroidism*.

The term *infantile hyperthyroidism* is intended to embrace only those cases of exophthalmic goiter occurring in children before ten years of age, since during that period of development the genital system is still in its expectancy. *Juvenile hyperthyroidism* is that form of thyrotoxicosis occurring from ten to fifteen years of age, during which period the genital system undergoes its development. We shall call *adolescent hyperthyroidism* the cases of thyrotoxicosis which occur from fifteen to twenty-five years of age, during which period the genital apparatus reaches its maturity, and we finally reserve the term *adult hyperthyroidism*, to the cases occurring after twenty-five years of age.

*Infantile hyperthyroidism* is comparatively rare, whereas the *juvenile form* is more frequent. W. H. Lewis, quoting Mayo's statistics, found one case of infantile hyperthyroidism for 300 adult cases operated for thyrotoxicosis. The youngest of his cases was four years old when it came under his observation, and the disease had already existed eighteen months. Infantile and juvenile hyperthyroidism follow, as a rule, a milder and shorter course than that of adult hyperthyroidism. Left alone, the condition gives, according to Sattler, a mortality of 4.5 per cent.

The symptoms most commonly observed in infantile hyperthyroidism are irritability, nervousness and tachycardia. The little patients seldom are conscious of palpitation; exophthalmos is rarely marked, and the ocular symptoms are usually absent. Tremor as well as vasomotory disturbances of the skin are present in moderate degree. Gastro-intestinal disturbances are usually quite marked. As a rule these young patients, especially those of infantile type, do not experience the profound muscular asthenia which is so often observed in adolescent and adult hyperthyroidism. They are able to participate in the activities of their young companions without undue fatigue. Sometimes, however, they get out of breath more easily. Thyroid hyperplasia is of moderate degree and is subject to variations. Vascular symptoms are present. In the

juvenile and adolescent forms of hyperthyroidism psychic disturbances and chorea may occur as complications. Glycosuria is seldom observed.

In overactive children when restlessness, irritability, egotism, selfishness develop, the possibility of hyperthyroidism should always be considered.

So far as treatment is concerned, usually ligation of both superior poles proves of itself curative. If the case is already quite markedly advanced, thyroidectomy may become necessary.



## CHAPTER XXXVI.

### THYROTOXICOSIS IN PREGNANCY.

THAT a woman afflicted with Graves's disease may become pregnant, or that thyrotoxicosis may develop either during or at least in connection with pregnancy, is a well-known fact. The point of interest does not lie therein. What we want to know is, how do these two conditions influence each other, and what shall be our attitude in these given cases?

The coincidence of pregnancy with Basedow is not frequent. Out of 15,000 women seen in the Maternity of Edinburgh by Halliday-Croom, only 1 case of exophthalmic goiter in pregnancy was seen. The other 12 cases which he reported were taken from his private practice, hence his conclusion that pregnancy and Graves's disease are oftener found among the rich classes than among the poor ones. Bonnaire came to the same conclusion, because out of 30,000 pregnant women he saw only 2 cases of exophthalmic goiter.

Seitz has collected 112 cases of exophthalmic goiter complicated with pregnancy from his own material, from literature, and from circular letters. He has carefully tabulated the menstrual history, the appearance of the first symptoms, the history of previous pregnancies, the therapy employed, and the results as far as mother and child were concerned. He found that hyperthyroidism was not affected one way or the other in 40 per cent of the cases. A very small number even improved during pregnancy. On the other hand, 67 out of 112 cases, namely, 60 per cent of the total, were made distinctly worse by gestation. In one-fourth of these 67 patients a serious menace as to health and life was the consequence of thyrotoxicosis; 7 patients died; in 5 cases therapeutic abortion, and in 11 cases, premature labor occurred. Three miscarriages, and 3 macerated fetuses were observed. In 7 cases thyroidectomy was performed during pregnancy. Bernard von Beck in 260 cases of Graves's disease and pregnancy said that he felt compelled to perform thyroidectomy in 5 cases, and in no case did he find it necessary to interrupt the pregnancy. As Gellhoun says, this is indeed a remarkable record and may be explained by the fact that these thyrotoxic conditions were secondary to previous existing goiters, since in the region where von Beck is working, goiter is endemic. Theilhaber found that the majority of coincident cases of pregnancy and Graves's disease

were made distinctly worse by the disease and that only the minority were improved by it. Kleinwachter and Hirst came to the same conclusion that Graves's disease is unfavorably influenced by pregnancy, and that it often has its origin in gestation. It predisposes the patients to uterine hemorrhages and may result in the death of the fetus. Such cases are often complicated with albuminuria. Whitridge Williams considers that pregnancy exerts a deleterious influence on Graves's disease; he found that tachycardia was greatly increased during gestation and lessened soon after labor. It has been, too, my experience in the cases of thyrotoxic pregnant women I have seen.

Doeja observed noticeable thyroid hyperplasia in 8 per cent of the pregnant women living in the Great Lakes region. He noticed furthermore, that 60 per cent of these women were made worse by pregnancy. Von Groff reported that 9 per cent out of 654 pregnancies developed goiter. He furthermore remarked that in eclamptic women, the thyroid enlargement was less marked than in goitrous, but that it was otherwise in normal pregnant women. In conjunction with this observation it is perhaps well to recall that Kendall was struck with the low percentage of total nitrogen in the form of urea in certain experimental animals which presented tetany and convulsions. The total nitrogen in the urine was high, but the percentage of nitrogen in the form of urea was very low. He furthermore observed that the amount of urea content in a given specimen of urine was considerably higher after standing than it was when voided. He found, for instance, that twenty-four hours after the urine was voided there was 400 per cent more urea than at the time of its emission.

In toxemia of pregnancy we have, too, a low urea and a high nitrogen content. In Kendall's opinion, it seems very probable that the mother substances of urea and the mother substances of nitrogen compounds are the same. If this substance is converted into urea the patient will live a normal existence. If, on the other hand, it is converted into other nitrogen compounds, toxic convulsions, toxemia, will result. There is every reason, in his judgment, for assigning the changes in the nitrogen of metabolism to certain ductless glands.

Markoe and Wing, examining 1586 pregnant women, found that in 6 per cent of the cases, the goiter could be traced back to the beginning of the pregnancy. In their experience the majority of goiters occurred with the first pregnancy. In multiparæ it usually appeared on an average with the fifth pregnancy. Watson, in 1918, reported 16 cases of toxic goiters complicating pregnancies. In all cases pregnancy acted as an activator.

We can consequently conclude that the majority of Graves's patients are made worse by pregnancy. Pregnancy must be regarded as a serious

complication in thyrotoxicosis. This is so true that Theilhaber has said when speaking of thyrotoxic patients:

"Girls, no marriage; women, no pregnancy; mothers, no nursing."

**Treatment.**—So far as Graves's disease is concerned, medical treatment should be given the greatest care and attention as soon as pregnancy is detected. Every form of treatment can be given a trial. Up to date the best treatment known is a dietetic, hygienic regimen and rest. In the numerous cases I have seen in consultation or otherwise, I have obtained, on the whole, satisfactory results with the use of my thyrotoxic and polyglandular tablets combined, if necessary, with judicial use of roentgen-rays handled by a competent roentgen-ray man. I should think that boiling water injections would be useful, too. The majority of cases so treated will be kept in fairly good condition and may be brought along to the full term of their pregnancy without too serious disturbances. At any rate, during the early period of pregnancy the treatment must be a *watchful waiting one*. If later, however, the condition of the patient grows worse, surgical intervention then becomes necessary.

Surgically, two questions arise: Shall we perform a thyroidectomy or shall we resort to an obstetrical operation? So far the trend of opinion seems to be in favor of the second alternative. If the fetus is viable, a premature Cesarean section may save its life, which very likely would be lost if allowed to go on to full term. If, on the other hand, the fetus is not viable and the condition of the mother is such as to necessitate a surgical intervention, the life of the child should be sacrificed without hesitation, since at any rate it is bound to be lost. In such cases the mother's life only should be taken into consideration.

I believe, however, that we should not wait until these thyrotoxic symptoms complicated with pregnancy have become so serious as to endanger the life of both the mother and the child. A timely thyroidectomy as I have performed in many instances seems to be the ideal procedure, as it not only wonderfully benefits the thyrotoxic condition, but also allows the pregnancy to go to full term, and thus saves the life of the child without undue risks for the mother. I have not yet experienced a death of the mother or of the child.

Basedow patients should be guarded against marriage, and especially against pregnancy. At any rate, before entering married life they should have thyroidectomy performed in order to safeguard them against any future exacerbations and to protect their future offspring. It is true that in severe forms of Graves's disease the chances for pregnancy are considerably reduced, because the sexual apparatus is in a state of hypofunction. This, however, is not always the case and pregnancies may occur even in very severe cases of thyrotoxicosis. When this is the case, "sterilization" of the women should be performed after pregnancy is over.

## CHAPTER XXXVII.

### ETIOLOGY OF GRAVES'S DISEASE.

THE fact that Filehnes, Walburton, Tedeschi, Dourdoufi and Bienfait by sectioning the restiform bodies were able to produce tachycardia, exophthalmos, hyperemia of the thyroid, etc., has given rise to a theory claiming that Basedow's disease is of bulbar origin. It must be said, however—and this is a very important point to remember—that the thyrotoxic, clinical picture did not take place, if previously or at the same time, thyroidectomy had been performed. The French school, especially Charcot, Trousseau, etc., and the German school, represented by Gerhardt, Buscham, Wickfield, Sattler, etc., have considered Basedow's disease as a neurosis of the entire vegetative nervous system. Notkine and Blum defended the view that Basedow's disease was due to a detoxicating insufficiency of the organism by the thyroid on account of functional insufficiency. Friedreich considered Basedow's disease as due to an abnormal enlargement of the coronary arteries of the heart, thus causing an increased blood supply to the cardiac muscle which in turn would cause an increased excitability of the nervous system. Gabriel Gauthier considered the thyrotoxic syndrome as of thyroid origin. Mannheim considered it as of central origin. Moebius claimed that Basedow was caused by poisoning of the blood by the thyroid products, and considered the forms frustes as well as the primary and secondary forms of exophthalmic goiter as all produced by the same cause, namely, the hyperfunction of the thyroid. Crile believes that it is a "philogenic" disease, caused by a disturbance of the entire motor mechanism in which the nervous system is primarily involved and in which the thyroid acts as an activator. Hart and Bircher believe that Basedow's disease is primarily of thymic origin. Klose, Lampe and Liesegang believe that the disease is due to *dysthyroidism*. Thus, as one can see, the theories concerning the etiology of Graves's disease are numerous, and I have not cited them all by any means.

The theory which up to date has rallied the greatest number of partisans is the theory of *hypersecretion* of Moebius, called *thyrotoxicosis* by Kocher, and *hyperthyroidism* by Mayo. According to these authors, Basedow's disease is caused by a surplus of thyroid secretion poisoning



the entire organism. This surplus may be caused either by an increased function of the thyroid or by thyroid feeding. This theory is indeed the one which tallies best with our present knowledge, and which seems to be best supported by the facts. It is simple and clear, but I am afraid that just because of this simplicity and clearness, it is insufficient. The more one studies this question, the more one becomes convinced that the problem is a complicated one; the more one tries to penetrate the secrets of Nature, the more one sees how intricate her ways are. As v. Hansemann says, "Nature does not know a cause, but causes." Indeed, if we consider an event in its simplest form, even though the determining factor seems to be obvious, how many other "preparatory" conditions are not necessary to allow the so-called primary cause to exert its effect? And so it is in medicine. Almost everyone will say, for instance, that tubercle bacilli are the cause of tuberculosis, yet, if truly they were the only cause, every living man would be tuberculous because it has been shown beyond doubt that everybody's organism contains tubercle bacilli. Fortunately, in order to allow tubercle bacilli to thrive, other "preparatory conditions" are just as necessary as the presence of the tubercle bacilli themselves, and only when all these conditions happen to be assembled, does tuberculosis develop. It is consequently wrong to say that tubercle bacilli are solely the cause of tuberculosis. One should say "tubercle bacilli are one among others, of the conditions necessary for the development of tuberculosis." If one of these "conditions" is absent, there will be no tuberculosis. Take, for example, Addison's disease. If tubercle bacilli were the only necessary requirement, again, almost everybody would have Addison's disease. This disease is too fairly frequent to be considered as the result of the mere accidental settling of tubercles in the suprarenal bodies; furthermore, the fact that the tuberculous involvement is bilateral, speaks, too, against such an explanation. The truth of the matter is that other conditions, secondary indeed, but just as necessary and important as the tubercle bacilli, must intervene before the invading tubercle bacilli can thrive in the suprarenal bodies. Exceedingly forceful in demonstrating this very thing is the hypothetical example mentioned by Sahli, that of a child who has been slapped in the face once by its teacher, and who develops soon after a tuberculous meningitis. At once the family concludes that the slap in the face was the cause of the tuberculous meningitis, hence a lawsuit for damages. "This lawsuit," says the defendant, "is ridiculous. Everybody knows that without tubercle bacilli, there is no tuberculosis, that if a tuberculous meningitis develops, the child must have had tubercle bacilli in his organism previous to the slap in the face, that slaps in the face are given every day without there occurring

a tuberculous meningitis, that finally there is no more relation between a slap in the face and tuberculous meningitis than there is between a bellyache and the moon." "All this may be very well," says the plaintiff, "but the fact remains that the child was well before, that he got sick soon after the slap in the face, consequently had he not been slapped in the face, he would not have developed a tuberculous meningitis." And no one will be able to convince the plaintiff to the contrary. He sees one cause: this cause suffices to explain the whole thing. He does not see, or does not want to see, that besides this apparent cause there are many others just as important, without which a tuberculous meningitis would never have developed, and that in this particular case the slap in the face was merely a coincidence.

And so it is for the etiology of Graves's disease. Of course the thyroid lesions still play the predominating role in the development of the disease. But this is not all; other conditions intervene; other factors play their part too, such as the nervous system, and the other organs of internal secretion. It is for this reason that I shall say that Graves's disease is a *thyro-neuro-polyglandular disease caused by a toxic thyroiditis*.

So far as the geographical and racial distribution of thyrotoxic goiter is concerned, the reader is referred to the chapter on "Geographical and Racial Distribution of Simple and Thyrotoxic Goiter in the United States." It was deemed more interesting to handle these two subjects together.

Let us proceed to try to demonstrate successively and separately the four members of the above proposition:

- A. The thyroid origin.
- B. The nervous origin.
- C. The polyglandular origin.
- D. The toxic thyroiditis.

**A. Thyrogenetic Origin of Graves's Disease.**—Arguments in favor of the thyrogenetic origin of Graves's disease are among the most numerous; they are derived from *clinical observation*, from *pathology*, from *experimentation*, and from the *results of surgical treatment*.

1. It was because he was struck by the antithesis which existed between the clinical symptoms observed in thyroid insufficiency and those seen in Graves's disease that Moebius concluded that the latter condition was due to a hyperfunction of the thyroid. Indeed, one cannot but be impressed in the same way after glancing over the masterful synopsis made by Kocher in 1902. It takes the two opposite conditions at their worst, and reads as follows:

HYPOTHYROIDISM.

Absence or atrophy of the thyroid gland.  
 Slow, regular pulse of small volume.  
 Absence of hot flashes, sensation of cold.  
 Indifferent, expressionless and lifeless look.  
 Small palpebral fissure, small eyes.  
 Bad appetite, slow digestion, constipation.  
 Reduced metabolism.  
 Thick, cold, dry, scaling skin.  
 Short, thick fingers with thickened terminal phalanges.  
 Great tendency to sleep.  
 Reduced sensibility and diminished sensory impressions.  
 Diminished mental and intellectual power.  
 Awkwardness and slow actions.  
 Stiffness of the extremities.  
 Short, thick, often deformed skeleton.  
 Slow, deep respiration.  
 Increase in weight.  
 Old appearance of the patient, even though young in years.

HYPERTHYROIDISM.

Diffuse hyperplasia of the thyroid.  
 Hypervascularization.  
 Rapid pulse, rather increased pressure, sometimes irregular.  
 Marked vasomotor disturbances. Patient is always too warm.  
 Very anxious, exceedingly mobile look with a rapidly changing expression.  
 Wide palpebral fissure and exophthalmos.  
 Often increased appetite, vomiting, diarrhea.  
 Increased metabolism.  
 Thin, warm, soft, moist skin, no scaling.  
 Long, thin fingers with pointed phalanges.  
 Insomnia and disturbed sleep.  
 Increased sensibility and increased sensory impressions.  
 Increased mental and intellectual activity, great psychic excitement, hallucinations, mania, and melancholia.  
 Restlessness and haste in movements.  
 Tremor but marked agility in movements.  
 Thin, slender skeleton.  
 Superficial, rapid, and slightly irregular respiration.  
 Loss of weight.  
 Rather youthful appearance, especially in the early stage of the disease.

Furthermore, Kocher found that phosphates are beneficial to hyperthyroidism, but are harmful to hypothyroidism; that a sojourn in high, cold climates is beneficial to hyperthyroidism, but harmful to hypothyroidism; that a sojourn at the sea is harmful to hyperthyroidism, but helpful to hypothyroidism. Certainly the antithesis between all these symptoms is forceful and speaks strikingly not only in favor of the thyrogenetic origin of the disease, but also in favor of the hyperthyroidism theory.

2. The fact that thyroid feeding is most injurious to the great majority of cases of Graves's disease, and produces, as a rule, only exacerbation of all the symptoms, must be interpreted as another proof of the thyrogenetic origin of Graves's disease, and of the hyperthyroidism theory. Since in hypothyroidism the feeding of thyroid extract is curative, it is logical to consider the bad results obtained from thyroid feeding in Graves's disease as directly due to the increased amount of thyroid secretion in an already saturated organism.

3. In cases where thyroidectomy has been performed in view of remedying the thyrotoxic condition, if a relapse of symptoms occurs, there is, too, a relapse of the goiter, and *vice versa*; hence another proof in favor of the intimate relation of the goiter with the clinical symptoms of the disease.

4. Another powerful argument is derived from the clinical observation that in many cases of secondary thyrotoxic goiters one can follow a gradual transition in the intensity of the symptoms going from the slightest form of thyrotoxicosis to the most fully developed picture of Graves's disease. Anyone who has had experience with goiters knows that this sliding of the scale is quite frequent. As Wölfler says, "It is easy to go progressively from a simple goiter to a well-marked case of Graves's disease, as for instance, goiter with tachycardia; goiter with tachycardia and tremor; goiter with tachycardia, tremor and exophthalmos; goiter with tachycardia, tremor, exophthalmos and digestive disturbances, etc., until we get the complete clinical picture of Basedow's disease." These cases, no matter if they are fully developed, or constitute only the fruste forms of Graves's disease, all recognize the same etiology; they are all dependent upon the thyroid intoxication.

5. Another proof in favor of the hyperfunction of the thyroid is the fact that exophthalmic goiter seldom occurs in regions where goiter is endemic, namely, where the thyroid is permanently and endemically in a state of hypofunction. Even when such endemic goiters become overactive, the worst they can do is to give birth to mitigated forms of hyperthyroidism such as thyrotoxic goiter-heart, nervousness, etc. They seldom reach the fully developed thyrotoxic clinical picture. As soon, however, as we consider regions where goiter is not endemic or mildly so, where consequently the thyroid gland has retained its full functional capacity, there Basedow disease becomes very frequent and severe in its forms.

6. If in order to obtain shrinkage of the gland, the thyroid is attached to the integuments by the operative measure known as *exothyropexy*, it is found that the thyrotoxic goiters show a far greater secretion than the simple goiter, hence the conclusion that the thyrotoxic goiter functions more than the simple one is obvious.

7. The fact, on the one hand, that a sudden hemorrhage occurring in an already existing colloid or cystic goiter may in some cases cause marked thyrotoxic symptoms, such as palpitation, great nervousness, tremor, gastro-intestinal disturbances, insomnia and even sometimes a moderate exophthalmos; and, on the other hand, the fact that all these symptoms will subside, as resorption of the hemorrhage goes on, and will finally disappear when the goiter has returned to its quiescent state again, or on the contrary, will increase progressively into a true case of Base-



dow's disease when the thyroid does not quiet down, all go to show that there is a relation from cause to effect between the pathology of the thyroid and Graves's disease.

8. The fact that Basedow's disease is found with an acute thyroiditis is another proof of the thyrogenetic origin of Graves's disease. This question will be discussed later in considering the relation between thyroiditis and Graves's disease.

9. The coexistence of thyrotoxic symptoms with malignant goiter has long since been known. Already in 1871 Tillaux mistook a sarcoma of the thyroid for an exophthalmic goiter. Carrel, out of 83 malignant goiters found 26 showing unmistakable thyrotoxic symptoms. Poncet and Bouveret saw a malignant goiter with a complete clinical picture of Basedow's disease, exophthalmos included. Delore and Alamartine, Kocher, myself, and I am sure every thyroid surgeon, have seen similar cases.

The thyrotoxic symptoms occur either after metastases have taken place or before. If they occur only after the tumor has metastasized, since we know that malignant metastases of thyroid tissue always retain their physiological secreting power, then it is logical to conclude that the symptoms of hyperthyroidism are due to the increased functioning surface due to the malignant tumor plus its metastases. If thyrotoxic symptoms occur before metastases have taken place, the hyperfunction may be due to the fact that the malignant portions of the tumor irritate the remaining normal glandular tissues and incite it to hyperplasia in the same way that intraglandular hemorrhage does: hence symptoms of hyperthyroidism as we see them sometimes after hemorrhage in simple non-toxic, cystic, or colloid goiters.

**Pathological Arguments.**—It is not enough to support our conclusions with clinical data. No matter how strong these clinical proofs may be, they alone would not carry conviction as well as they would if they were supported by convincing pathological evidence. Let us see what pathology teaches us.

We have seen in the chapter dedicated to Basedow Struma that hyperplasia of the thyroid is one of the most constant findings in thyrotoxicosis, so constant that Kocher has said, "No goiter, no Graves's disease." It is indeed true that in the great majority of cases an enlargement of the thyroid is present. As a rule it is obvious. It would be a mistake, however, to believe that thyrotoxicosis necessarily means that thyroid hypertrophy is always clinically detectable. There are cases of thyrotoxicosis, even very severe ones, with only a slight hyperplasia or none at all. In a great many cases, this hyperplasia, which is clinically "apparently" absent, is nevertheless present. This is proved time and time again because at the time of the operation the gland is found to

be larger than normally. Furthermore, it must not be forgotten that hyperplasia of the thyroid in Basedow fluctuates with the stage of the disease itself, that the time when the patient comes for examination may be very well the period in which hyperplasia is in its incipient stage, or in which the thyroid has returned to its quiescent state, or is undergoing atrophy: hence the impression then that there is no enlargement of the thyroid. If, however, a careful history is taken, one will almost always learn that at one time or another there was some enlargement. So far, so good. But there is better. We have seen that the microscopic changes in the gland are characteristic of Graves's disease; and that hypertrophy and hyperplasia of the cellular elements, thinning of the colloid, more or less marked desquamation and cytolysis, and the presence of foci of lymphoid tissue throughout the parenchyma are its chief characteristics. These changes have been found by such a great number of authors that they certainly cannot be considered as merely accidental; they must bear a direct relation to the clinical syndrome of Graves's disease. Before we have the right, however, to consider these histological changes as specific for Graves's disease, we should prove that these changes occur: (1) constantly in that condition; (2) that they occur in no other condition but Graves's disease. So far as the first condition is concerned, we have concluded with L. B. Wilson (*loc. cit.*): "By assuming that the symptoms of the true exophthalmic goiter are the results of an excretion from the thyroid, and by attempting to determine the amount of such excretion from the pathological data, one is able to estimate in a large series of cases the clinical stage of the disease with about 80 per cent of accuracy, and the clinical severity of the disease with about 75 per cent of accuracy. It would therefore appear that the relationship of primary hypertrophy and hyperplasia of the parenchyma of the thyroid to true exophthalmic goiter is as direct and constant as is primary inflammation of the kidney to the symptoms of Bright's disease. Any considerable finding to the contrary I believe to indicate either inaccurate or incomplete observations on the part of the pathologist or clinician, or both."

We have further seen that even if there is no appreciable macroscopic hypertrophy of the gland, these typical histological changes just spoken of could be found either diffusely distributed throughout the parenchyma or in the isolated areas, provided one takes the trouble to make seriated slides. The few rare cases of thyrotoxicosis where no histological changes are present, must most likely depend upon the disturbance of some other organs of internal secretion, as the thymus, for instance.

So far as the second proposition is concerned, we must admit, too, that similar histological changes may once in a while be met outside of thyrotoxicosis in the form of adenomatous formations. But we must

not forget that *similar* does not mean *identical*, and that it is by no means certain that the function of such adenomatous formations as are sometimes seen in non-toxic conditions is identical with that one of the hyperplastic epithelium seen in thyrotoxicosis. Even suppose that it were, then it very likely constitutes only one of the many "preparatory conditions" without which the disease cannot develop, as it requires more than the mere presence of the tubercle bacilli to cause tuberculosis.

On the whole, we can consequently admit that these anatomical changes in the thyroid are specific of the disease.

**Experimental Arguments.**—Experimentation, too, has furnished its contingency of proofs in favor of the thyrogenetic origin of Graves's disease. Although a number of attempts to reproduce experimentally in animals the clinical syndrome of Graves's disease have proved failures, nevertheless, a great many investigators, whose authority and scientific honesty cannot be questioned, have succeeded where others have failed. The doubt as to the feasibility is no longer permissible.

Injected subcutaneously or given by mouth, thyroid extracts have more or less the same influence on *thyroidectomized animals*: trophic disturbances gradually disappear, myxedema becomes less marked, the skeleton grows again, metabolism increases, the blood formula reverts to its normal type, and in short, the animal gradually becomes normal. This thyroid opotherapy is not only beneficial, but is also necessary because if it is not kept up, the animal sinks again into its previous myxedematous condition. On the other hand, fed to *normal animals* in overdoses or for too long a period of time, the thyroid extract becomes harmful. Tachycardia, tremor, dyspnea, extreme agitation, brilliancy of the eyes, fever, polyuria, and in many instances, exophthalmos are the results. Why such a difference? Because to the first series of animals we have given them something they had not, something they needed. To the second, we have added a surplus of thyroid product when they already had plenty of it; we have saturated their organism with it, and it is that surplus which has become injurious. Experiments proving such contention are numerous. Not only can we reproduce the whole clinical syndrome, but also the characteristic changes in the blood, such as leukopenia, hyperlymphocytosis, hyperpolynucleosis, diminished viscosity and coagulability of the blood, etc. Ballet and Enriquez have obtained the thyrotoxic syndrome accompanied by exophthalmos, after daily intravenous injection of thyroid products into animals. Krauss and Friedenthal, injecting intravenously into rabbits the thyroid products dissolved in salt solution, observed the thyrotoxic symptoms characterized by rapid pulse, nervousness, tremor, exophthalmos, widening of the palpebral fissure, and dilatation of the pupils. Tedeschi obtained in dogs the complete clinical picture of Basedow's disease,

namely, tachycardia, exophthalmos, and goiter by the same process. Cunningham and Hoennicke, experimenting upon rabbits, and Edmunds, upon a monkey and dogs, have, too, reproduced the clinical syndrome of Graves's disease with exophthalmos. Baruch, in 1912, used for his experiments non-toxic parenchymatous and colloid goiters. Soon after removal these goiters were ground finely so that they could be injected subcutaneously or into the peritoneal cavity. With this method he reproduced experimentally in dogs, rabbits, rats, a typical Basedow's disease characterized by nervousness, emaciation, loss of hair, diarrhea, tachycardia, glycosuria, typical blood changes, and in a few instances marked exophthalmos. Three of such dogs with exophthalmos were shown by him before the Breslau Surgical Society. One of these dogs as the result of lagophthalmos developed an ulcer of the cornea.

Luthi and Verebeli, after producing artificially a congestion of the thyroid gland, were able to observe in the thyroid the typical histological changes which are so characteristic of Graves's disease. They observed at the same time tachycardia and an increased excretion of nitrogen and phosphorus.

Tatum and Mills observed that if rabbits were kept for a week or longer in a cold storage box, the thyroid would show signs of hyperactivity, such as increased epithelium and thinning of the colloid. However, if the animals were kept in a warm room, signs of thyroid hyperplasia were absent.

But the experiments carrying with them the greatest conviction were undertaken by Klose in 1909. Convinced that the unsuccessful attempts made by others to obtain the fully developed clinical symptoms of Graves's disease were due to the fact that dried and powdered gland had been used, which had most probably lost many of its properties, he used the thyrotoxic goiters in their fresh state as soon as they were removed surgically from patients. These glands were submitted to a squeezing process and the juice so obtained, called *Press-saft* or "*Pressed juice*" was then injected into the jugular vein of dogs and without anesthetic. Klose found that the best results were obtained whenever he used "highly nervous fox terriers." Soon after the intravenous injection the blood pressure sank from 100 to 85 millimeters of mercury. The tachycardia became exceedingly marked, pulse was at times scarcely countable, respiration became irregular, tremor, sweating, gastro-intestinal disturbances were very pronounced, fever rose high, and exophthalmos in many instances became very apparent. Albumin and sugar were found. The typical blood changes were present. This condition lasted for a few days, then subsided and the dogs became normal again. These experiments undertaken on a large number of dogs always showed the same constant results. The intensity of the symptoms observed was dependent upon



the toxicity of the Press-saft as shown by the clinical symptoms: the most intense toxic symptoms were produced by the Press-saft from primary thyrotoxic goiters. The secondary forms or Basedowified goiters were less toxic. The toxicity of this Press-saft gradually diminished after standing, and after a period of five or six days became powerless. Mechanical shaking, drying of the gland, heating of the juice, destroyed very quickly its toxicity. If to a normal thyroid or goiter which proved itself non-toxic, a solution of iodide of potash was added, the toxicity of the Press-saft at once became apparent, lasted for a few days and then disappeared. In injecting enormous doses of Press-saft from non-toxic goiters or from other organs such as the liver, etc., Klose was unable to obtain the Basedow symptoms.

Kendall claims that thyroxin, which he regards as the active principle of the thyroid, when injected into animals produces the toxic symptoms similar to the ones observed in hyperthyroid states.

Efforts, although few, have been made in order to demonstrate in the blood the existence of some toxic substances which would exist only in Graves's disease and in no other condition, and which might be regarded as of thyroid origin. Most of these tentatives have been fruitless; not all of them, however. See the Kottmann test. There is no doubt that more investigation should be made in that direction, and that with appropriate laboratory methods, we shall be able to isolate many of these substances some day.

That there exists in the blood serum of Basedow patients a substance which produces a marked cardiac depression is certain. Gley, in 1911, observed that each time a serum of Basedow patients was injected into animals, there was at once a marked depression in the blood-pressure, lasting, it is true, only for a short time, but nevertheless constant. He showed, too, that a first injection of potent exophthalmic serum conferred a tolerance of such nature that subsequent injections of the same serum produced little or no effect. Blackford and Sanford have repeated Gley's experiments and have obtained the same results. Hence the conclusion that the blood serum of Basedow patients contains a powerful *depressor substance*. This depressor substance is not only present in the serum of Basedow patients but is also present in the thyroid gland itself, and its depressive power is in direct proportion to the severity of the disease. In simple non-toxic goiters this substance is not present at all.

The acetonitrile test of Reid Hunt was applied to the serum of Basedow's disease. It is known that with this method, mice which have been fed with thyroid extract become at least ten times more resistant to acetonitrile than the controls, hence the conclusion that blood serum, if it truly contains thyroid products in excess, should render mice treated with it more resistant to acetonitrile than normal mice. This experiment

has been performed and the results show that the surmise was correct; indeed the blood serum injected into guinea-pigs rendered them also much more resistant to acetone-trile than the control. Hence the warranted conclusion that blood serum of Basedow patients contains an excess of thyroid products.

Arno Ed. Lampe, experimenting with the Abderhalden method upon the blood of twenty-five Basedow patients, came to the conclusion that this blood contains thyroid, thymic, and even ovarian principles which do not exist in normal individuals.

Finally, in 1917, Kendall came to the conclusion that, in order to obtain a so-called hyperthyroid reaction, hypertrophy of the thyroid is one result that must be obtained. Accompanying this an activity of the suprarenal cortex is essential. Unlike the thyroid whose active constituent is *thyroxin*, and unlike the suprarenal cortex, it cannot be demonstrated in normal animals except after the gland has been stimulated. In order to have the suprarenal cortex manifest its activity, it seems essential to have a vigorous oxidation going on within the animal. Electric stimulation, fear, etc., will act in the same way. When such is the case, larger amounts of the enzyme which acts on ammonium carbonate are found in the blood, in the suprarenals and in the tissues. The chemical reaction which seems to take place, according to Kendall, is a reaction of the ammonium carbonate into something which is not urea, and which he calls *substance-X*, and should be an intermittent compound between ammonia and urea. This substance, highly toxic to the organism, is a compound called by Kendall *preurea compound*, and in his judgment this preurea compound is concerned in the production of toxic symptoms which he observed after injecting in dogs amino-acids.

**Arguments Derived from Thyroid Opothrapy in Human Beings.**—But besides all these experiments in animals, there is a whole series of clinical observations in human beings which have the full value of experiments, and which show, too, that there is a direct relation between the thyroid and Graves's disease. These results are seen when a prolonged and injudicious thyroid opootherapy is resorted to.

In a myxedematous patient who had ingested 92 grams of thyroid extract, Beclere noticed a marked tachycardia, tremor, exophthalmos, rise in temperature, increased perspiration, etc. Boynet reported the case of a student who during a period of eight days absorbed 6 to 8 thyroids of sheep daily. He soon developed swelling of the thyroid, palpitation, tremor and an extremely advanced nervous condition which subsided only after the medication was stopped. Combe reported the case of Gagnebin, a friend of mine, who, while a medical student, absorbed daily one lobe of sheep's thyroid for a period of about two weeks. At the end of that time palpitation had become violent, fever and abundant

sweating were present, tremor was so intense that he could not rise nor carry his food to his mouth, and exophthalmos had become very marked; the experiment was interrupted and the symptoms gradually subsided. Nothaft reports a very demonstrative case of a man who was in good health and who undertook, on his own initiative, to take in a few weeks a thousand thyroid tablets of five grains each in order to reduce his obesity. He developed a typical Basedow with goiter, exophthalmos, tremor, sweating, loss of flesh and glycosuria; the medication was stopped and ten months later the patient was normal again. Ferrarini saw the case of a woman who had taken thyroid as an antifat cure; she had taken 6 to 8 tablets of thyroid daily for two months. After that time she lost 8 kilos, complained of vertigo, palpitation and insomnia. She nevertheless increased the quantity of thyroid and then became very nervous, pulse 150, diarrhea alternating with constipation, psychic disturbances, hallucinations, etc. Kocher saw that the return to normal of the blood of a myxedematous patient followed directly the improvement of the patient's condition. When the patient was clinically cured, the blood formula was normal. If an overdose of iodothyron were given, the typical changes of the blood would recur, accompanied this time by diminished coagulability of the blood and by thyrotoxic symptoms such as tachycardia, nervousness, tremor, etc. Is it possible to give a more striking proof that myxedema is due to hypothyroidism, and Graves's disease presumably to hyperthyroidism?

A greater number of cases could be cited to prove the same contention, and every surgeon who has had dealings with the goiter question, has, more than once, seen patients who on account of a prolonged and injudicious use of thyroid extract or iodine, had converted a simple non-toxic goiter into a thyrotoxic one.

French undertook to study the comparative toxicity of different tissues in animals susceptible to thyroid feeding, the object being to discover whether the effects of commercial thyroid extracts when administered, are specific or whether similar effects could be produced by other animal tissues prepared and administered in the same way. "Whether the toxicity is due to products of decomposition, or whether it is due simply to the great amount of proteid matter ingested by an animal unaccustomed to such a diet." His conclusions were as follows:

1. Thyroid in the forms used, fresh, stale and desiccated, either commercial or laboratory prepared—contains a substance that is decidedly toxic for some animals.

2. The other animal tissues used, brain, liver, spleen, kidney and skeletal muscle, give no evidence of toxicity when prepared and fed in the same way in equal or even larger quantities.

3. While the study does not indicate the nature of the toxic substance,



it would seem to show conclusively that it is not due to protein in the food. This seems to prove conclusively that the toxic symptoms found are peculiar to the thyroid and to no other organs.

Massage of a non-toxic goiter, as shown by Brieger; radiotherapy, as shown by Chvostek, De Castello and Schmidt; electrical treatment, as seen by myself, have at times, by stimulating the thyroid gland, produced an exophthalmic goiter.

Plummer, in 1921, claimed that pure hyperthyroidism can be produced in a person by the administration of thyroxin, and that the syndrome thus produced cannot be distinguished from the hyperthyroidism resulting from an overactive adenoma of the thyroid. In each case, either the discontinuance of the thyroxin, or the operative removal of the adenoma ends the syndrome and the patient rapidly recovers his normal condition with a normal basal metabolic rate.

It cannot be denied that all these experiments carry with them great weight which, added to that afforded by the clinical and pathological data, becomes singularly powerful.

**Surgical Argument.**—The best of all the arguments in favor of the thyrogenetic origin of Graves's disease is given by the results of surgical treatment. The number of cases treated by this method now reaches well into the thousands; we have consequently plenty of material to draw our conclusion from. As seen in studying the results of surgical treatment, this latter method produces 50 to 85 per cent of the cures in fully developed cases of Graves's disease and nearly 100 per cent in the ones taken in their early stage. Now, no matter how little value one attaches to statistics, he cannot but be impressed by these figures. We have seen, too, that *x*-rays, radium, injection of boiling water, etc., in short, any method intended to directly attack the thyroid gland in itself, with the purpose of reducing its size, and hence of reducing its function, produces good results, although temporary, as a rule. Why should it be so if there were no direct relation between Graves's disease and the thyroid, and why should it be so if the relation were not an intimate one? This is so true that Riedl has said, "We would cure all Basedow cases if we could be allowed to remove the entire thyroid gland." How often have we surgeons marvelled at the magic effect of a simple ligation or a thyroidectomy upon numbers of cases of Graves's disease which had resisted every medical treatment. I know very well that, unfortunately, it is not so for every case, because the etiology of Graves's disease is a most complex one, as we shall see later. But the fact nevertheless remains that in the great majority of cases the thyroid must be the main guilty factor, because by removing a part of it we not only put a stop to the progress of the disease, but also cause its regression. In the early stages the effect is rapid and sure. In the later stages the result will depend



upon the damage done to the nervous system, to the glands of internal secretion, to the heart, kidneys, liver, etc. We cannot expect, of course, to restore to normal a permanently diseased organ. And yet even in advanced cases the surgical treatment is beneficial; rarely does it remain without effect.

It has been said that the good results due to the surgical treatment are of psychic order. It may be partially so in a few cases of Graves's disease complicated with hysteria, but this is certainly not the rule. The results we attain are in direct proportion to the quantity of thyroid gland put out of function. Why should it be so strikingly constant if our results were due to psychic interference? As Crile says very properly: "If psychic influences can cure the disease, then the surgeon alone possesses this influence because all surgical cases have been unsuccessfully treated by internists first. This compliment to the superior psychic power of the surgeon, unhappily, we cannot conscientiously accept, because the surgeon is unable to favorably influence his patient except at the time of his contact with the patient on the operating table, and at that time his patient is unconscious."

It has been said, too, that the good results obtained by surgical treatment were due to the forced "rest in bed." How many patients do we not operate who have been taking in vain the "rest cure" for months and years under the direction of possibly the best internists? Why should we accomplish in two or three weeks what internists failed to obtain in months and years of the same "medicine." The argument is poor indeed.

If we consider all the evidence gained from the clinical, pathological, experimental and therapeutic data with a fair and unprejudiced mind, we are bound to recognize that the first member of our proposition made in the beginning of the chapter, namely, that Graves's disease is a thyrogenic disease, is abundantly demonstrated. Although I am willing to admit that the "irrefutable, peremptory argument" is not yet at hand, and that the one which might be considered as such, as the experiments of Klose, should be confirmed, nevertheless the weight of "circumstantial evidence" is so strong that I am sure that there is no jury in the world which would let a criminal go free on the evidence of charges similar in strength. Coupled with the excellent results which we obtain with surgical treatment, this evidence will still lead us to proceed in the same line of treatment until we get something better, and no matter what the adversaries of the thyrogenetic theory say, we will repeat with Galileo, "E pur si muove." "And still it moves."

**B. Nervous Origin.**—Let us discuss the second member of our proposition, the *nervous origin*. As we know, there are some authors who consider the central nervous system as the cause of exophthalmic goiter,

and others who regard that disease as a neurosis similar to the one seen in hysteria and epilepsy; while some authors believe that its origin is primarily due to a disturbance of the sympathetic system, and again, some others, to that of the vagus system. Then, too, others consider it only as a reflex due to some irritating influence taking its origin in the uterus, intestines, etc.

That the glands of internal secretion in general are directly influenced by the central nervous system is abundantly proved. For example, the puncture of the fourth ventricle causes diabetes, and the irritation of the subthalamie region causes an increased function of the adrenals, as shown by Ascher. The section of the restiform bodies, according to Filehne and Warburton, causes hyperemia of the thyroid gland, exophthalmos, tachycardia, etc. L. B. Wilson, in 1918, using the goat as an experimental animal, exposed the superior cervical sympathetic ganglia and stimulated this either electrically or by injections of various forms of bacteria and thus obtained the histological picture in the thyroid gland similar to the one found in thyrotoxic goiter. Hence, his conclusion that Graves's disease is due to overstimulation of the thyroid *via* the sympathetic.

Cannon by irritating the sympathetic obtained a definite exophthalmos in dogs.

In certain psychoses, in neuroses, in catatonia as shown by Roenfeld, Kaufmann, Paganini, the metabolism is greatly disturbed, the nitrogen excretion is greatly diminished, and the phosphorus and calcareous elimination greatly increased. The same is true in Graves's disease.

We must therefore recognize that the nervous system plays a very important part in exophthalmic goiter; whether this influence is primary or secondary is, however, another matter.

To be sure, in Graves's disease the nervous system is unstable. There is a certain train of nervous symptoms such as emotionality, irritability, restlessness, instability, which forms an integral part of the clinical syndrome of that condition and which is just as typical of the disease as tachycardia, tremor, exophthalmos. etc. These nervous symptoms are sometimes the dominant feature in the whole syndrome. To consider them, *a priori*, and always as the primary cause of the disease seems to me, however, quite premature. We have nothing at hand to substantiate this conclusion; we have very much against it. Moreover, experiments show that the nervous symptoms follow administrations of thyroid extract and do not precede it. I know too well, and I have admitted it previously, that an unstable nervous system is a "predisposed terrain" on which thyrotoxicosis might easily graft itself. When I see certain young, nervous, irritable and unstable individuals I cannot help but look upon them as future candidates for Graves's disease. Possibly

you will say that this is the best proof that the disturbed nervous systems of such individuals is primarily the cause of their thyrotoxicosis. "Post hoc, ergo propter hoc." Possibly so. I am willing to admit that it can be so sometimes, but in many other instances, might it not be that a number of these cases of irritable and unstable nervous equilibrium are only latent forms of hyperthyroidism which go unrecognized, and which may never go any further or which may some day explode into a typical Graves's disease? In fact I know that in some cases it is so, as I have operated on some such cases with the most gratifying results. And so have all who have busied themselves with thyroid surgery.

In studying the nervous symptoms in connection with Graves's disease we came to the conclusion that the other forms of nervous disturbances as melancholia, psychoses are purely accidental. They must be considered as associated complications grafted upon a predisposed terrain; heredity, psychic as well as physical stigmata, are found in the psychoses non-complicated with Graves's disease just as well as in thyrotoxicosis complicated with mental disturbances and psychoses. We have seen, too, that Graves's disease supervening in such predisposed terrain is bound to favor the eclosion of psychoses, and *vice versa*; thyrotoxicosis will evolve more easily in individuals whose nervous system is already unbalanced. There is no need to insist further.

Great stress is laid by the partisans of the nervous theory of Graves's disease upon the element of fear, psychic shock, fright, etc., in order to prove the nervous origin of Basedow's disease. It is true that there are cases of Basedow's disease whose incipency has been very sudden. Trousseau, for instance, reports the case of a woman whose father died, and who from sorrow developed in the space of a night a true case of Graves's disease with exophthalmos, vascular goiter, etc. Dieulafoy saw a woman who, after violent emotion, developed very rapidly an exophthalmic goiter. In such cases there seems to be less doubt that the nervous system is the primary cause of the trouble. These lightning forms, however, are rare. They nevertheless carry great evidential weight with them as they show that there exists an intimate relation between the thyroid and the nervous system, and that Graves's disease may possibly take its origin in a primarily disturbed nervous system.

There is another class of cases, however, where the starting-point of the disease is referred to a psychic shock due to a runaway horse, an automobile accident, railroad wreck, etc., but there thyrotoxicosis has become noticeable only weeks or months after the occurrence. For these cases the nervous origin of Graves's disease is more doubtful, because the time elapsed from the accident to the development of the disease is quite long. It must not be forgotten that if one goes into the history of these cases carefully he will usually find that long before the

accident occurred there was a latent period during which a few Basedow symptoms were already present. They may have been only barely sketched; that is enough: the nervous system of these patients had already lost its normal equilibrium, hence the ease with which the shock of psychic order affected it. Indeed, one cannot but be impressed by the fact that often the psychic shock to which the origin of the disease is ascribed is truly insignificant; at any rate would be insufficient to upset a normal nervous system. Why is it so? Either because at the time of the accident the disease was already in a period of incubation, so that the psychic shock shaped it into its definite form and intervened as the "puller of the trigger," or because this nervous system was in ordinary conditions unstable and barely able to hold its equilibrium, and only required an insignificant cause to tip it over the border-line. This latter possibility appears that much the more plausible since Klose, in order to obtain the best results in reproducing experimentally the clinical picture of Graves's disease, resorted to highly nervous fox terriers. It is further corroborated by the fact that the same shock will affect one and not another. For instance, did all the survivors of the "Titanic" disaster, or did all the soldiers of the great war develop Graves's disease? Not by any means, yet they all underwent the same ordeal.

Aside from a few exceptions, it must be positively proclaimed that in the great majority of cases of Graves's disease psychic shock cannot be accused of being the causative factor simply because it was not present. Surely no one is going to claim, for instance, that all the secondary or Basedowified goiters are of psychic origin, that a runaway accident or a railroad wreck is at the bottom of all the primary forms of Basedow's disease, or that a scare by a burglar or a rape by a negro is responsible for the cases of Graves's disease following acute infections, acute thyroiditis, and, furthermore, that disappointed love must be looked for in all the cases of Graves's disease occurring at the time of puberty and menopause. In the great majority of all these cases there is no apparent cause at all for the development of the disease. To claim that these cases are primarily of nervous origin is simply to make a statement founded upon no proof.

A painstaking analysis, made by Drysdale in 1917, of 17 cases of Basedow's disease, alleged to have been caused by trauma, shows quite conclusively that the condition must have for its development suitable soil, and that without this, exophthalmic goiter cannot occur. In other words, there must be an inherent predisposition to the malady. It is also his opinion that the degree of physical violence had little, if any, significance, and that whatever is caused in this respect arises from shock and emotional storms acting through an unstable nervous and psychic constitution. Trauma becomes, therefore, only a determining factor.



This, he thinks, will adequately explain why so few cases develop following physical violence and why so many of the ordinary cases arise from influences which are in no manner related to traumatism.

**Vegetative Nervous System.**—Life is controlled by two great nervous systems: (1) the *sensory-motor* nervous system, which serves the senses commanded by the will; (2) the *vegetative* nervous system supplying the organs with smooth muscles, such as the gastro-intestinal tract, the blood-vessels, the gland ducts and the skin, all the glands of internal and external secretion, the heart, and the muscles of the genital apparatus. Anatomically, these two great systems cannot be distinguished readily, inasmuch as their nuclei lie close together both in the brain and in the spinal cord. Their principal difference lies in their peripheral makeup. The sensory-motor system has but one neuron between the nerve centers and the periphery, while the vegetative system has ganglion cells interposed in the course of the nerves. These ganglionic interruptions vary in their locations, some being on the path of the nerves, such as the celiac ganglion, some at the periphery, as is the case of the heart and intestines.

In turn the vegetative system may be divided into two other great systems, the *sympathetic* and the *autonomic* systems.

The *sympathetic* includes the fibers arising from the middle and lower parts of the thoracic and from the upper part of the lumbar cord. The *autonomic* includes the fibers which arise from the midbrain, the bulb and the sacral cord. The nerve plexus from the midbrain segments finds egress mostly by way of the oculomotor nerve pathways. The ones from the bulbar segment proceed by way of the facial, the glossopharyngeal and principally the *vagus*. The nerves from the sacral segment of the cord are contained in the pelvic nerve which supplies the descending colon, the sigmoid, anus, bladder and genital apparatus.

In normal conditions the sympathetic and the autonomic systems are antagonistic; what one accelerates the other moderates, and *vice versa*; for instance, the cardiac action is accelerated by the sympathetic and diminished by the *vagus* system; intestinal peristalsis is paralyzed by the sympathetic and accelerated by the *vagus* system. The welfare of the organisms depends upon the harmony and intelligent working of the two systems; as soon as one of them becomes aggressive and overdoes, then the equilibrium is broken and disturbances follow.

The same system, be it sympathetic or *vagus*, contains acceleratory and moderatory fibers. For example, besides cardiac acceleratory fibers, the sympathetic contains cardiac moderatory fibers, and besides moderatory fibers, the *vagus* contains also acceleratory fibers. It is true that the acceleratory fibers found in the *vagus* and the moderatory fibers contained in the sympathetic are far less numerous than their antagonists, yet they exist, and must come into play in some way or another. This

shows that the same system can be acceleratory and moderatory at the same time, a fact very important to remember, as it shows that the duality of function of an organ is possible. This dual function most likely occurs through the influence of hormones acting electively and exclusively upon each set of fibers.

This notion of "duality of function" of the same organ is an exceedingly important one to remember. It must be safe to say that the nervous system cannot be the only one to have this peculiarity, but that other organs must certainly share the same property. This must be especially true for the organs of internal secretion. And so it is. As shown by Eliot, small doses of adrenalin produce a vasodilatation of the blood-vessels, whereas in higher doses it produces a vasoconstriction. Pituitrin increases the contractions of the gravid uterus of a rabbit, whereas it paralyzes the non-gravid. Iscovesco isolated from the glands of internal secretion various lipoids, each one possessing a definite property, although coming from the same gland; in that case the function instead of being dual may be manifold. This principle being accepted, at once the horizon widens and facts which at first seemed to contradict themselves, as for instance the simultaneous presence of hypothyroidism and hyperthyroidism symptoms, become intelligible.

Excitation of the sympathetic nerve causes tachycardia, exophthalmos, alimentary glycosuria, enlargement of the palpebral fissure, and increased metabolism. On the other hand, excitation of the vagus causes sweating, vomiting, diarrhea, lymphocytosis.

We know that Cannon by anastomosing in cats the right phrenic nerve with the right cervical sympathetic, thus causing a volley of nerve impulses each time the animal breathed, observed in four of the cats that survived, symptoms and metabolic changes very similar to those observed in thyrotoxic goiter of man. Hence, Cannon's conclusion that the thyroid is subject to that division of the nervous system brought into play by emotions.

Adrenalin produces the same effect as does the excitation of the sympathetic, namely, an excitatory action whenever the sympathetic fibers are excitatory, or paralyzing whenever they are inhibitory. On the other hand, small doses of pilocarpine or muscarine stimulate the vagus system; at the same time they stimulate the sympathetic fibers which supply the sudoriparous glands. Atropine paralyzes the vagus system and the sympathetic fibers supplying the sudoriparous glands. Thus, in Eppinger and Hesse's judgment these pharmacological reactions differentiate the two systems fundamentally, and, furthermore, give one the right to conclude that they are antagonistic.

Since by feeding animals or human beings with thyroid extracts we obtain results which resemble very much the ones seen after the adminis-

tration of pilocarpine or muscarine, such as vomiting, diarrhea, lymphocytosis, eosinophilia, sweating, respiratory disturbances, etc., it is logical to conclude that there exists in the thyroid, substances, or better, *hormones*, whose effects are similar to that of pilocarpine, and which act electively upon the vagus system. Furthermore, since a number of other symptoms seen in Graves's disease are exactly similar to the ones obtained by irritation of the sympathetic, such as tachycardia, alimentary glycosuria, enlargement of the palpebral fissure, exophthalmos, increased metabolism, etc., and since the ingestion of thyroid extract produces the same troubles, it is rational to conclude that either the thyroid contains one or more hormones acting electively upon the sympathetic system, or that the thyroid hormones act upon other organs such as the suprarenal bodies, whose adrenalin then influences the sympathetic system.

But there is something more. Small doses of pilocarpine which in normal individuals will have little or no effect, may produce intense symptoms in other individuals, hence the conclusion that the vagus system of the latter subjects is normally in a state of *hypertonus* because an excitant which normally would remain without effect is sufficient to cause in them marked symptoms. Hesse and Eppinger say that these individuals whose vagus system is in a state of constant hypertonus are *vagotonic* and call *vagotrope* the substances which act upon the vagus system. These vagotonic individuals are normally sensitized to vagotropic substances; at the same time they remain more or less refractory to substances which ordinarily act upon the sympathetic system.

The same is true for the sympathetic. Substances which in normal individuals will cause little or no effect upon their sympathetic system will prove very active in certain other individuals. Again, according to Hesse and Eppinger, the sympathetic system of the latter individuals is in a state of constant hypertonus; these individuals are *sympatheticotonic*, and the substances which act upon the sympatheticotonic individuals are sensitized to *sympatheticotrope* substances. At the same time in such individuals the vagotrope substances given in large doses remain without effect; they, too, seem to be inhibited. The vagotonus is determined by the excess secretion of the vagotrope hormones accompanied at the same time by a diminished secretion of the sympatheticotrope hormones. The sympatheticotonus is caused by an excess secretion of the sympatheticotrope hormones accompanied at the same time by a diminished secretion of the vagotrope hormones.

The thyroid consequently contains sympatheticotrope and vagotrope hormones. In Basedow's disease both varieties of hormones are increased and both act electively upon the sympathetic and vagus systems, hence the mixed symptoms take their origin in the sympathetic as well as the vagus disturbances. The fact being admitted by



Eppinger and Hesse that there are patients who are normally vagotonic or sympatheticotonic, it will naturally follow that in such individuals some of the thyroid hormones will center their effects mostly upon the already sensitized system: if the vagus, for instance, happens to be the one which is in constant hypertonus, vagal symptoms will be more marked than the sympathetic ones, hence we will have marked vomiting, diarrhea, sweating, etc., whereas, on the other hand, if the sympathetic is the one already sensitized, the poisonous hormones of the thyroid will center their effect mostly upon that system, hence the predominance of tachycardia, exophthalmos, glycosuria, etc. Purely vagotonic or sympatheticotonic cases are rare; as a rule they are mixed. Consequently the degree of vagotonicity or sympatheticotonicity of the organs will to a certain extent determine the nature of the thyrotoxic syndrome and its intensity, hence the explanation why thyrotoxic cases are not all alike, and why the entire symptom-complex of Graves's disease is not always met in one case. Thus it will be understood that it is not necessary to have a large goiter in order to have a severe Basedow, if one happens to be normally vagotonic or sympatheticotonic or both. Thus it will be understood, too, that it is not necessary that the whole gland be hyperplastic, but that isolated areas of localized hyperplasia will suffice to cause the thyrotoxic syndrome, because these areas will send what Kocher in the forethought of his genius called "Basedow impulses," and which are nothing else than lipoids acting electively upon already sensitized organs. Thus this will finally, to a certain extent at least, as other factors intervene, afford a reasonable explanation for the fruste forms of Graves's disease.

Let us conclude: The nervous system takes in the production of Graves's disease a very active and important part. Cannon, in 1914, was able to reproduce experimentally some of the symptoms of exophthalmic goiter in cats by constant stimulation of the thyroid through the sympathetic system. If it is true that the nervous system may in a few cases be primarily affected, in the remainder of the cases it is only secondarily involved.

**C. Polyglandular Origin.**—This is the third member of our proposition. If one takes a bird's-eye view of the symptoms due to disturbances of each one of the organs of internal secretion separately and compares them with each other, besides the typical and characteristic symptoms due to the pathology of the gland itself, there is a train of secondary symptoms which occurs in almost every disturbance of these organs. Example: Suppose we deprive a young woman of her ovaries: besides the complete amenorrhea and loss of sexual appetite, we shall observe hot flashes, sweating, palpitation, moderate tachycardia, nausea, glycosuria, vomiting, nervousness, cutaneous eruptions, depressive states, and



sometimes temporary insanity. And, again, take Addison's disease, for instance; there, too, besides profound myasthenic symptoms characterized by an intense feeling of excessive fatigue, going sometimes into a state of complete adynamy, and besides melanodermy, there is a group of more general symptoms present, such as complete loss of appetite, vomiting, diarrhea, alternating sometimes with constipation, polyuria and polydipsia, headache, loss of sleep, nervousness, states of depression, low blood-pressure, flabby heart, irregularity of menstrual function, and sometimes complete amenorrhea, and so on. The same is true in a general way for the pathological conditions of the other organs of internal secretion.

If we compare these clinical symptoms with the ones seen in Graves's disease we are forced to admit that a number of them found in the latter condition seem to be common to diseases of other organs of internal secretion, although in every instance the organ primarily involved is an entirely different one. This must mean, consequently, that there is between all these organs a functional interrelation. And so it is, as shown by the pathology and by experimentation. No one organ is independent of the other organs. There is no one organ driving the other organs exclusively, but rather do the organs drive each other reciprocally. There is here no solar system around which everything else gravitates. Our organism is not an autocracy but a democracy. To be sure, some organs are more important than others, but they are, nevertheless, dependent upon the less important, and *vice versa*. Whenever one becomes pathologically involved its derangement repercussions upon the function of the others. There is, in other words, a functional solidarity among them all. This solidarity is not only functional, but is compensatory, too. For example, if one of the hemispheres of the brain is removed, there is a compensatory hyperideation in the other hemisphere. When a large bloodvessel becomes obstructed for some reason or another, and incapable of carrying the blood through the normal channel, a collateral circulation takes place in order to relieve the flood; and of this no better example can be given than that of the caput medusæ resulting from obstruction of the portal vein. If one kidney is removed the other one compensates its loss by hypertrophy and increased function, and so on. The thyroid does not make an exception to these laws. Let us see if we can base our views upon something tangible.

**Thyroid and Hypophysis.**—Boise and Biedl found a marked hypertrophy of the hypophysis in two cases of myxedema and in one of sporadic cretinism. Schönemann and Comte found an hypertrophy of the hypophysis whenever the thyroid was degenerated or atrophied. Rogowitsch found a constant hypertrophy of the hypophysis after complete thyroidectomy had been performed. Guerrini and Delille after treating various

animals with thyroid extract found that there was more or less constantly an hypertrophy of the hypophysis. Hyperemia of the hypophysis has been found in connection with Graves's disease. It is logical to admit that the hypophysis participates functionally in the production of the thyrotoxic syndrome because vasomotory disturbances, variations of temperature, increased sensation of thirst, and polyuria are commonly seen in disease of the hypophysis. The disturbed metabolism of fat and the cutaneous eruptions seen in Graves's disease are likely due to disturbances of the hypophysis. Alquier and Hallion, after feeding rabbits with hypophysis extract, found vasoconstriction of the thyroid gland and finally shrinkage of the whole gland.

In Guerrini's, Salvioli's and Carrier's opinions, the hypophysis has an antitoxic function and regulates blood-pressure and the cardiac rhythm.

Placing the thyroid gland of etherized dogs in a metal oncometer, being careful not to injure the bloodvessels nor the relation of the gland to the surrounding structures, Isaac Ott and J. C. Scott, in 1913, observed that a solution of 0.275 cc infundibulin, the active principle of the posterior part of the pituitary, "had the most marked effect of all the glands in reducing the volume of the thyroid." This diminution at times was preceded by a momentary increase of its gland volume immediately after the injection. When the gland was diminishing the general blood-pressure was rising, while the pulse-rate was lessened for a few seconds and then rose.

The dried anterior glandular part of the pituitary was rubbed up with distilled water and part of the infusion injected. This increased the volume of the gland, an effect directly opposite to the action of the posterior nervous lobe. While the thyroid was enlarging from the injection of the pituitary, the general arterial tension fell for a moment and then rose above normal. The pulse-rate was temporarily lessened and then became normal.

Hallion, in 1909, noted that an infusion of the whole pituitary reduced the volume of the thyroid. On the other hand, Trautmann, in 1916, claimed that there is an inner physiological relationship between the hypophysis and the thyroid and that complete or partial thyroidectomy on goats causes an actual pathological alteration of the blood and of the pituitary. The alterations that occur in the latter organ are mostly of the degenerative type.

In 1919, Allen reported that if the hypophysis be removed from the larvæ of amphibians, development of the thyroid gland is retarded, and that thyroid removal causes hypertrophy of the pituitary.

E. R. Hoskins and M. Hoskins, in 1920, reported the results of their study of the interrelation of the thyroid and of the hypophysis in the

growth and development of frog larvæ. They found that when a preparation of the lobe of beef hypophysis was given to thyroidless larvæ, which would otherwise have remained in the larval form more or less indefinitely, a beginning metamorphosis occurred within twenty-four hours and became nearly complete by the time the animals were killed. From these experiments they concluded that the hypophysis in its relation to the amphibian metamorphosis is derived from the thyroid, as was shown by Gudernatsch. These authors regard the results obtained as due to stimulation of the natural congenital metabolic processes. It is very doubtful, in their judgment, if the action of the antipituitary substance is due merely to its iodine content, since other tissues with traces of iodine would not produce the same effect as the pituitary. Consequently, these authors concluded that the hypophysis and the thyroid are closely related physiologically, and can, to some extent, function vicariously. Their investigations, as well as those of others, develop the following findings concerning the thyroid and the hypophysis:

I. Removal of the thyroid hastens growth, causes hyperplasia of the hypophysis and prevents metamorphosis.

II. Removal of the hypophysis retards growth of the thyroid, prevents metamorphosis and retards development of the cutaneous pigment.

III. Feeding thyroid or hypophysis (or iodine) to normal larvæ hastens metamorphosis.

IV. Feeding thyroid or hypophysis (or iodine) to thyroidectomized larvæ brings about metamorphosis.

V. Feeding iodine to larvæ with both thyroid and hypophysis removed causes metamorphosis.

As seen by all these pathological and experimental data, there is on the whole little doubt of the existence of some sort of specific relation between the thyroid and the hypophysis.

**Thyroid and the Genital System.**—That there is a relation between the thyroid and the genital apparatus, is shown by the fact that the great majority of Basedow patients are women, and that the disease is influenced materially by menstruation, pregnancy and menopause. The constitutional difference between man and woman is due solely to the genital apparatus. More than men, women are all their lives under the constant influence of their genital system. This influence begins at the time of puberty, keeps up with each menstruation, and only stops at the menopause. During all these periods not only the nervous system is jeopardized, but the entire organism is in a state of constantly changing equilibrium, hence the tendency for women to develop Graves's disease more frequently than men.

As we have seen in studying the disturbances of the genital system, in Graves's disease menstruation is often irregular, and not infrequently



totally absent. This total amenorrhea may remain permanent and may then give rise to a premature menopause. Hand in hand with these genital disturbances there often goes hypoplasia of the genital system. This atrophy is found, too, in hypothyroidism. When myxedema occurs in adults it is not infrequent to see a complete reversion to sexual infantilism marked by atrophy and impotence. For instance, Lanz reported the case of a man who had become myxedematous ten years after thyroidectomy; the testicles became markedly atrophic. Ceni noted a marked diminution in the production of eggs in thyroidectomized hens. Parhon and Goldstein consider the thyroid and ovaries as antagonistic, whereas Charrin and Jardry claim that they are synergetic.

By placing the thyroid in a metal oncometer as explained in the section on thyroid and hypophysis, Isaac Ott and Scott found that an infusion of fresh ovaries of a pregnant cat rubbed up with normal saline solution augmented the volume of the thyroid, a fact which was previously noted by Hallion in 1909. While the thyroid was enlarging from the ovarian injection the blood-pressure rose slightly for about six seconds and then returned to normal. The pulse-rate was not changed.

When fresh corpus luteum of the pig was rubbed up with normal saline solution and injected per jugular it increased the volume of the thyroid. When the thyroid was enlarging the general blood-pressure fell for a few seconds and then rose to normal. The pulse-rate was normal. Consequently, in their judgment the enlargement of the thyroid at menstrual periods is due to the action of corpus luteum upon the thyroid.

Marine, in 1917, observed that the removal of the ovaries in animals probably tends to decrease the activity of the thyroid. There is no evidence, however, that this is a direct effect. The various attempts to establish a direct relationship between the thyroid and the ovaries by a comparison of the influence of extracts on metabolism have given negative or doubtful results. Through the study of cryptorchids and the experiments of ligating the vas deferens, it has been definitely established that the interstitial linin-rich cells of the testes largely determine the male secondary sexual characters. In the case of the ovary it is not possible to separate the oögenic cells from the interstitial cells, but the attempts thus far made suggest that these cells play a very important and similar role in the secondary sex characters of the female.

Nevertheless, it is a well-known fact that in man thyroid hyperplasia is many times (6 to 8) more common in the female, during and after adolescence, than in the male, during and after adolescence. Up to this period sex makes no difference in the incidence. Congenital goiter is not influenced by sex and in all the lower animals sex likewise has no influence, the incidence remaining the same at all periods of life.

Removal of the ovaries is usually accompanied by hyperplasia of the



thymus, spleen and lymphoid apparatus. Nothing is known about the cause of such reaction.

Isaac Ott and Scott claimed that infusion of *human placenta* increased the volume of the thyroid, while it lowered the blood-pressure slightly for only a few seconds, which then returned to normal. The pulse-rate was unchanged.

Furthermore, infusion of 0.0324 gram of dried *prostate*, although not affecting the pulse-rate but momentarily lowering the blood-pressure, nevertheless caused a fall in the volume of the gland after the pulse and arterial tension became normal. They have also shown that prostate has the most activity of all glands with internal secretion in augmenting the volume of erectile tissue in the male. Hallion has confirmed this.

Infusions of dried *orchitic extract*, although diminishing momentarily the rate of the pulse and arterial tension, caused a slight decrease in the volume of the gland after the blood-pressure and pulse-rate returned to normal.

**Thyroid and Mammary Gland.**—Isaac Ott and Scott observed that infusion of mammary gland produces an enlargement of the thyroid, lowers the arterial tension for a few seconds and that it then returns to normal. The pulse-rate is unchanged.

**Thyroid; Pancreas; Adrenals.**—There is no doubt that there is between the thyroid and the pancreas an intimate relation. The disturbances in the metabolism of carbohydrates so often seen in Basedow's disease must be attributed to a disturbed function of the pancreas. The same is true for the disturbed resorption of fat which gives rise to fatty stools. Chvostek was among the first in determining these facts by showing that certain cases of Basedow were caused by disturbances of the pancreas, and that the symptoms would retrocede after pancreas opotherapy. Kohn and Peiser confirmed Chvostek's conclusions, basing their statement upon postmortems of thyrotoxic patients in which undoubted pancreatic lesions were found. Eppinger, Falta, Rudinger, Grey and De Sautelle have noted that glycosuria could be produced experimentally in dogs by giving them large doses of adrenalin; and that glycosuria does not take place at all if thyroidectomy has been performed. This will explain why myxedematous patients can stand very large doses of sugar without showing alimentary glycosuria. Falta has reported one case in which after thyroidectomy marked hypertrophy of the islands of Langerhans was found.

Rudinger, Falta and Eppinger have tried to show that the thyroid, the pancreas, and the adrenals were intimately related and exerted a reciprocal action one upon the other (Fig. 78). According to them the pancreas inhibits the thyroid and the chromaffin system, the adrenals inhibit the pancreas and stimulate the thyroid, while the thyroid also

inhibits the pancreas and stimulates the adrenals (Fig. 78). Consequently, the thyroid and the pancreas on the one hand, and the chromaffin system and the pancreas on the other hand, are antagonistic, whereas the thyroid and the chromaffin system are synergetic. From this it follows that the hyperfunction of one will have as a consequence the hyper- or hypofunction of the others as the case may be. Hyperthyroidism, consequently, must produce an insufficiency of the pancreas and a hyperfunction of the adrenals. This will explain why in pancreatectomized animals the excitability of the dilatator muscles of the iris is greatly increased, and this is most likely on account of the increased output of adrenalin. The same is true for animals overfed with thyroid extract, and the same is likewise true for Basedow patients, who often react by widening of the pupils after the instillation of a few drops of adrenalin. The well-known reaction of the adrenalin test might also support that point of view. In athyroidism and hypothyroidism, the

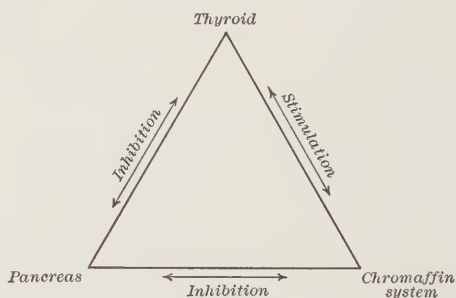


FIG. 78

function of the thyroid being diminished, its inhibiting power on the pancreas is *ipso facto* diminished also; hence the increased function of the pancreas which in turn results only in an increase of the inhibitory power of the pancreas upon the thyroid, thus forming a vicious circle in which the pancreas takes more and more the upper hand. At the same time, as the exciting power upon the chromaffin system by the diminished thyroid is reduced, and as the inhibitory power of the pancreas upon the chromaffin system is increased, we must likewise have a diminution of adrenal function.

Since normally the pancreas peptonizes the proteins through its trypsin, saccharifies the amylaceous substances through its amylopsin, and saponifies the fat through its steapsin, and as, on the other hand, these various functions in hyperthyroidism are inhibited, so we must expect to find that the metabolism of carbohydrates is greatly diminished, and we must consequently expect to find loss of peptones, glycosuria and fat in the stools. And so it happens quite frequently. On the other hand,

the opposite must be true in hypothyroidism: indeed, it is a known fact that in that condition the tolerance for carbohydrates is greatly increased.

Kojima has shown that feeding of thyroid extracts to rats causes definite changes in the pancreas such as atrophy of the alveoli and alveolar cells, changes in their staining capacities, diminution of their zymogen content, and increased mitochondria. Cessation of the thyroid feeding restores the pancreas to its normal state, while, on the other hand, thyroidectomy increases the physiological activity of the pancreas.

This feature seems rather well explained by Hirotoshi Hoshimoto, who observed that the continuous feeding of thyroid extracts containing 0.4 mg. of iodine per gram to white rats of both sexes produced a profound decrease of diastatic activity of the pancreas. This diminution of the diastatic power is due to the actual diminution of the diastase content of the pancreas. The amylolytic action of the diastase seems not to be disturbed. Hoshimoto also observed, or rather confirmed, the reports of Kojima, in 1916, who stated that there was a marked diminution of acidophile granules within the pancreas cells. The diminution of the diastatic power is in direct proportion to the amount of thyroid secretion. Furthermore, Hoshimoto observed that after thyroid feeding the intestinal juice becomes milky, less yellowish, and thinner, showing the diminished diastatic activity. Diminution of appetite seems to be in direct proportion to the diastatic power, the appetite being much increased when the diastatic power is very much diminished. In extreme cases the intestinal juices contain considerable quantities of fat. In many instances the pancreas is found much enlarged. In such cases the pancreatic diastase was often decreased even when the amount of fat consumed and the intestinal diastase was augmented. This decrease cannot be ascribed to general metabolic perturbations, since it really antedates any evidence of such. It is rather ascribed to stimulation of the diastatic secretions from the pancreas. Inasmuch as Hoshimoto observed under the microscope many fat drops and crystals (stained by Sudan III) in the feces excreted by some thyroid-fed rats, the pancreas diastase being extremely decreased, while in the feces from the normal rats fed on a bread and milk diet no fat drops were observed, he concluded that steatorrhea is caused by hyperthyroidism, namely, by excess of autacoid and deficiency of external secretion of the pancreas. Hoshimoto believes that this result is due to direct stimulation of the thyroid autacoid upon the biological action of the pancreas thus forced to discharge its ferments more quickly than in normal conditions.

Isaac Ott and Scott, on the other hand, claimed that infusion of the pancreas has but little effect upon the thyroid volume.

There seems to be no doubt that there appears to be a close interrelation between the *adrenals* and the *thyroid*. Hoskins reported that the

administration of thyroid extract to newborn guinea-pigs increases the size of their adrenals, while pregnant adult pigs, similarly fed, gave birth to offspring possessing reduced size of adrenals. Here, as we see, one observation rather contradicts the other. Ott and Scott claim to have obtained an increased adrenin output following intravenous injection of thyroid extract. It is fair to say, however, that they obtained similar results with extracts of the other glandular organs.

Herring, too, observed an increased output of adrenin after feeding cats with large doses of raw thyroid. He furthermore found that small doses of thyroid extract administered to white rats would cause hypertrophy of the adrenals and an increased adrenin output. The cortical substance was somewhat more hypertrophied than the medulla. Cannon and Cattell have come to the conclusion that adrenin injections enhance the secretory power of the thyroid, as does splanchnic stimulation, which in their judgment is the equivalent of increased adrenin secretion. Marine found that removal of a great portion of the adrenals causes an unmistakable thyroid hypertrophy. The same is observed in Addison's disease.

The adrenalin test raised into routine clinical use by Goetsch shows, too, to a certain extent, that the adrenals are called into play in cases of thyroid hyperfunction. For further information see the chapter on "Adrenalin Test."

Krauss and Friedenthal have shown that normal human blood serum has no effect upon the frog's eye; if, however, thyroid extract is injected a marked mydriatic power of the serum is found. This reaction is very likely due to an increase in the adrenalin content of the blood, or at least to an abnormal amount of sympatheticotonic substances of some sort. Caro confirmed these statements. In using the Meltzer-Ehrmann test, many authors and myself often found an increased adrenalin content of the blood of Basedow patients; in many instances, however, this increase is not present. Kostlivy, treating per os rabbits with thyroid substances, noted a marked increased mydriatic power of the serum proportionate to the dosage. At the autopsy the adrenals of these rabbits showed marked hypertrophy. In hypothyroidism no changes in the adrenals are found.

In conclusion it may therefore be said that the weight of evidence seems to show that there exists an undoubted interrelation between the thyroid, the pancreas, and the adrenals. The adrenals and thyroid stimulate reciprocally; the thyroid and pancreas inhibit each other, while the pancreas and adrenals are antagonistic.

**Thyroid and Liver.**—Hoshimoto found that after eighteen hours' fasting almost 90 per cent of the glycogen disappears from the liver of normal rats. Following decreased assimilation of carbohydrates in the alimentary canal, glycogen diminishes rapidly in the liver. The disappearance



of glycogen from the liver as the result of thyroid feeding was observed in rats with poor appetites. These consumed only a little bread and milk per day, but it was still evident in rats in the later stage of thyroid feeding, when their appetites were regained or rather augmented. This indicates that the amount of fat consumed is more than double and that the pancreas was already enlarged, and contained greater quantities of diastase than in normal rats while the diastase activity of the intestinal juice was normal. It seems evident that the diminution of the pancreas diastase takes only a small part, or none, in decreasing glycogen in the liver. This may be ascribed to the direct influence of the thyroid upon the liver or to the increased general metabolism stimulated by an excess of thyroid autacoid.

**Thyroid and Thymus.**—This subject is extensively treated later in the section on thymus. There, too, we shall find that an interrelation between the thyroid and thymus must undoubtedly exist.

**Thyroid and Parathyroids.**—According to Tage Iversen, no parathyroid lesions are found in Graves's disease. On the other hand, Alquier and Hallion, after feeding animals with parathyroid extract, observed marked histological changes in the thyroid, resembling the ones seen in Basedow's disease, whereas feeding with hypophysis seemed to produce exactly the opposite picture.

Isaac Ott and J. C. Scott, in 1913, observed that infusion of parathyroids sometimes increased and sometimes diminished the volume of the thyroid. The blood-pressure sank for a few minutes, then rose to normal. The pulse-rate was unchanged.

Noel Paton, in 1917, claimed that there is a functional distinction between the thyroid and the parathyroids, and explained that the comparatively large proportion of survivals after complete thyrothymectomy in rabbits was due to the fact that parathyroid tissue nearly always occurs in the thymus of these animals.

S. Vincent and Arnason, in 1920, studied the functional relation between the thyroid and the parathyroids, and came to the conclusion that there is no distinct hypertrophy of the parathyroids following thyroidectomy. In none of the parathyroids did they find any distinct trace of vegetative formation, nor did they find, as previously reported by Vincent and Jolley, in 1905, Halpenny and Thomson, in 1909, any signs showing that parathyroid tissue was converted into thyroid tissue.

**Thyroid and Lymphoid Organs.**—Among the lymphoid organs involved in thyrotoxicosis, the *spleen* is not so commonly involved. It never reaches a very large volume, but can sometimes be easily outlined by percussion and can be palpated. A. Kocher found it in about one-third of all his cases. The cervical lymph nodes are very frequently involved. At the same time it is not so uncommon to find an enlargement

of the tonsils and adenoids. The lymphoid tissue of the intestine, especially of Peyer's patches, is enlarged.

**Conclusions.**—Although it is still difficult to gain a clear insight into this complicated mechanism of the organs of internal secretion, there cannot be any doubt as to the functional interrelation of all these organs. The thyroid forms one very important ring of the polyglandular chain. Its pathology repercusses upon the other organs of internal secretion which in turn react upon the thyroid, hence a *vicious circle*.

Summing up, we are forced to conclude that, although the thyroid gland plays the most important part in the production of Graves's disease, we must nevertheless concede that other factors intervene at the same time, such as the nervous and the polyglandular systems. Hence my conclusion: Thyrotoxicosis is a *thyroneuropolyglandular disease*.

Let us see now if we can gain some information as to how the thyroid changes take place and what the intimate working of the process is. In short let us try to demonstrate that thyrotoxicosis, in the last analysis, is a *toxic thyroiditis*. With this in view let us study first the iodine-Basedow and then see what relation exists between Basedow's disease and thyroiditis.

#### IODINE-BASEDOW.

The use of any form of iodine preparation may cause a group of symptoms known as *iodism*. This condition is mostly characterized by sneezing, running of the nose, sensation of constriction of the throat, bronchitis, stomach and intestinal catarrh, conjunctivitis with abundant lacrymal secretion, headaches and skin eruptions. In the beginning the tongue, mouth and pharynx are dry; later, however, abundant salivation takes place. These symptoms are due to the fact that iodine is eliminated through the mucous membrane and skin, and that some patients are more sensitive than others to its influences, or that they may have some sort of idiosyncrasy for iodine. This form of iodism is benign and mostly harmless; very exceptionally it may lead to acute edema of the glottis. Ordinarily it subsides as soon as the iodine treatment is discarded, and no ill effects are felt from it afterward. As seen this has nothing in common with the clinical picture known as hyperthyroidism.

An entirely different condition, although less widely known, is that of a certain form of iodine intoxication which occurs once in a while in connection with iodine treatment of goiter and which closely resembles the clinical syndrome seen in thyrotoxicosis. It is characterized by nervousness, tachycardia, tremor, palpitation, insomnia, gastro-intestinal disturbances, depressive conditions, marked loss of flesh, and a profound asthenic condition. In many instances, exophthalmos occurs. Rilliet, of Geneva, was the first, in 1895, whose attention was called to this form

of intoxication and regarded it as a sort of idiosyncrasy. He called it *constitutional iodism*. Since then similar observations have been made frequently and the condition has become well known to the clinicians. Breuer called it *iodine-Basedow*, and that denomination has been adopted by everyone.

Iodine-Basedow occurs with predilection in people of middle age, between thirty and forty; in young individuals the course of the condition is much more severe. Something very peculiar is the fact that some patients developing iodine-Basedow may have used iodine preparations several times previously and during more or less long periods without ill effects; then some day, for no apparent reason, the use of possibly only very small doses of iodine has been enough to cause the iodine-Basedow. Women are more often affected with it than men. The condition, as a rule, starts two or three weeks after beginning the iodine treatment, grows worse as long as the medication is kept up, and usually disappears gradually after the iodine medication has been discarded. It takes, as a rule, several months before the patient's condition becomes normal again, sometimes years. Even then there sometimes remains a tendency to palpitation, nervousness, etc. In other instances, instead of regressing the condition progresses gradually and develops into a severe case of Graves's disease; a fact which I have observed more than once.

A fact worthy of notice is that hand in hand with the appearance of the iodine-Basedow goes a reduction in the size of the thyroid gland. Later, however, if the iodine-Basedow should grow into a true Basedow the thyroid gland will enlarge again.

**Is There any Relation between Iodine-Basedow and the Quantity of Iodine Absorbed?**—In a great many cases the smallest doses of iodine are sufficient to produce iodine-Basedow; cases are known where the mere use of tincture of iodine applied once or possibly twice to the skin or gums was sufficient to cause the condition. On the other hand, it is known, too, that some individuals may stand the most prolonged, large doses of iodine without the slightest ill effect except possibly some iodism. We are consequently forced to conclude that the quantity of iodine is in itself irrelevant.

C. C. Wholey, in 1918: "Observed a most pronounced instance of acute iodism in a cerebral spinal syphilitic after but two days of rather mild iodide administration; in addition to the distress of the iodism this patient's slightly enlarged thyroid suddenly increased to an alarming size, and what had been a moderate pulse became one of extreme tachycardia. Tremor was marked and exophthalmos was present in spite of the greatly swollen lids resulting from the iodism. This patient's blood and spinal fluid were strongly Wassermann positive at the time."

The time which elapses from the beginning of the intake of iodine to the time when the symptoms of iodine-Basedow develop is variable; ordinarily iodine-Basedow occurs ten to fifteen days after the beginning of the iodine medication; in some instances, however, it may begin only weeks after the iodine medication has been stopped.

It has been observed that in countries where goiter is endemic, iodine treatment is very apt to cause an iodine-Basedow. Fleishmann has shown that susceptibility to iodine varies not only with each individual but also with regions: for instance, persons living in Geneva or Vienna are more susceptible than others living in other cities; 68 per cent of the patients seen in Basel, 23 per cent in Berne, and 3.7 per cent in Berlin when treated with iodine showed symptoms of iodine-Basedow. Why such a difference? Nobody knows.

Iodine-Basedow resembles so clearly the ordinary Basedow that we are forced to admit that both conditions are alike and are due to the same cause, namely, to hyperthyroidism. There is between them only a difference of degree. The iodine-Basedow which might be called *alimentary hyperthyroidism* bears to the ordinary Basedow the same relation that alimentary glycosuria does to diabetes. The first form is usually transitory; the second is more permanent, but both forms apparently recognize the same cause, no matter by what mechanism they occur.

There can be no doubt that iodine-Basedow is due to the disturbed metabolism of iodine. We have said before that whenever an iodine-Basedow begins to develop, there is at the same time a concomitant reduction in the size of the thyroid gland. It is true, however, that after a while the thyroid returns to its previous size and often exceeds it. What does this mean? It can signify but one thing, namely, that the thyroid gland is reducing its size by throwing off into the blood circulation a certain amount of its content. What can this content be if it is not the "colloid" itself, and where can the gland throw it, if not into the general circulation? In other words, iodine stimulates resorption so that the organism finds itself rapidly flooded with thyroid products. As the process goes on, however, the thyroid increases its secreting power by reduplication of the functioning parenchyma: hence, again, increase in volume of the thyroid. We know, on the other hand, that the "colloid secretion of the thyroid gland is formed mostly by thyroxin," which has a great affinity for iodine. How shall we bring them together and set forth a suitable explanation for the origin of iodine-Basedow?

One fact seems impossible to deny, namely, that the whole problem seems to hinge upon a defective metabolism of iodine. This is proved by the occurrence of iodine-Basedow after iodine medication, and by the fact that Basedow glands contain a lesser amount of iodine than any other form of goiter or normal thyroid. It is further corroborated by the fact



that thyroid products are toxic in direct proportion to their iodine content. That much is certain.

Another thing, too, seems to be more than probable: it is the fact that inorganic iodine as such is more or less inert; in order to be utilized by the organism, and in order to become useful or harmful, it must be combined with some albuminous substances. This will explain why inorganic iodine alone is inactive in hypo- and especially in athyroidism; in order to become therapeutic iodine must be combined with the thyroid products whose activity increases in direct proportion to their iodine content. It would seem that in ordinary conditions where a surplus of iodine is present in the body, the organism should not be worse off for it, as the thyroid and the other organs presiding over the metabolism of iodine ought to dispose of it very quickly. In some instances, however, for some reasons still unknown to us, matters go differently. Is it because of "special disposition," "idiosyncrasy," be it temporary or permanent, of the individual toward iodine, or because the great oxidizing power of the iodine directly activates the epithelial elements and drives them to overfunction, *or is it not because iodine causes a toxic thyroiditis?* We know that in iodine-Basedow the histological changes are the same as the ones seen in any other form of toxic or bacterial thyroiditis. Hyperemia of the gland takes place; cellular hypertrophy and hyperplasia occur; the thick colloid, rich in iodine, undergoes liquefaction and is quickly absorbed and thrown into the circulation under the form of an iodized albuminous substance, mostly thyroxin. Inasmuch as undoubtedly the thyroid has lost its power to metabolize iodine in the right way, it works at top speed in order to eliminate it, or to convert it into an absorbable product, hence hyperplasia, increased function, and "thyroid diarrhea," as Kocher so graphically pictures it. Very likely the iodine goes through and irritates the thyroid just as undigested food goes through and irritates the intestines. On the other hand, as shown by Oswald, the thyroxin even in very small doses increases markedly, and for a long time, the excitability of the vegetative nervous system, be it sympathetic or autonomic; consequently this increased amount of thyroid secretion, being constantly poured into the blood circulation, lowers the threshold of the nervous system, thus increasing its susceptibility and excitability. If it so happens that the nervous system has already been sensitized to these iodized thyroid products, at once the reaction will be intense: the thyroid products will markedly influence the nervous system, which in turn will "fire back" by influencing the thyroid gland. Thus, a vicious circle becomes established; the thyroid drives the nervous system and the nervous system drives the thyroid. This will go on until one of the two gives out, or until one of the two connecting links is broken, as by thyroidectomy, for instance.

We feel consequently warranted in considering the true iodine-Basedow as a toxic thyroiditis causing a toxic irritation of the great vegetative nervous system. The primary lesion, however, is found in the thyroid.

#### RELATION BETWEEN BASEDOW'S DISEASE AND THYROIDITIS.

The relation between infectious diseases and thyrotoxicosis is more than merely accidental. It is a relation of cause to effect. Indeed, a number of instances may be cited to show that there is a direct relation between the infectious process and the development of Graves's disease. Almost every infectious disease, as typhoid, articular rheumatism, scarlet fever, influenza, syphilis, tuberculosis, etc., is known to have been followed some time after by the thyrotoxic syndrome. Gilbert and Castaigne reported a case of a young girl, aged fifteen years, who during the course of typhoid fever developed a moderate thyroiditis, and a month later showed the classical symptoms of Graves's disease. Reinhold saw a patient who, during an attack of influenza, developed an acute thyroiditis, one lobe being more involved than the other. Three months after the patient developed a classical Basedow's disease. Curiously enough hypertrophy of the thyroid gland was most marked on the same side on which thyroiditis had taken place. De Quervain saw a patient who during repeated attacks of articular rheumatism developed a moderate degree of thyroiditis accompanied by unmistakable symptoms of Graves's disease. The case of Breuer's is classical. His patient was taken suddenly sick with an acute thyroiditis developed in the left lobe of the thyroid. However, four or five days after, everything subsided; a few weeks after the patient began to show symptoms of exophthalmic goiter which rapidly became so severe that seven months later he died from the consequence of his thyrotoxicosis. Postmortem showed in the left lobe of the thyroid a small encapsulated abscess which proved to be of staphylococcus origin.

D. D. Gletneff reported 9 cases of acute strumitis and thyroiditis followed by Basedow's disease. One of them was a child, aged eleven years. Another one was a young woman, aged twenty-four years, who, after typhoid fever, developed a severe exophthalmic goiter which caused her death a few months after.

I once knew a young physician, who, one summer evening while in perspiration, sat on his porch and got chilled. During the night he complained of intense pain in the neck. When I saw him the following morning he was in a state of complete physical collapse, utterly unable to stand or to walk, had a marked tremor, palpitation and tachycardia.

The whole thyroid was acutely inflamed; the right lobe being manifestly larger than the rest of the gland. The gland was very hard and exceedingly painful to pressure, temperature was  $101^{\circ}$  F. During the following five or six days the condition grew worse, palpitation, tachycardia, tremor and gastro-intestinal disturbances being exceedingly troublesome. The left lobe and isthmus reached about three times, and the right lobe, about four times their normal size; the whole gland remained exceedingly painful and hard; faint vascular symptoms developed in it. Graefe and Dallrymple symptoms and a moderate degree of exophthalmos became apparent. The patient during all this time remained exceedingly nervous and could not sleep. After a while, however, the symptoms gradually subsided, and after several months the patient regained his health.

I saw a young woman who after a massage treatment for a colloid goiter of the right lobe, and after a sore throat, developed an acute strumitis. Besides the thyroid symptoms such as swelling, extreme pain on pressure, hard consistency, and with a temperature of  $102^{\circ}$  F., she also had marked thyrotoxic symptoms characterized by palpitation, tachycardia, extreme nervousness, tremor, insomnia, unquestionable Dallrymple symptoms, a moderate exophthalmos, etc. After a week everything subsided, the thyrotoxic symptoms included.

I have had under observation a young nurse who had always been in good health, although rather high-strung and having a moderate-sized goiter. While nursing in the hospital, she was taken sick with an acute tonsillitis which lasted two weeks. During that short time the thyroid increased materially in size, and the thyrotoxic symptoms became very marked. After tonsillitis had subsided entirely the patient was a nervous wreck; pulse was 150 to 165, tremor intense and generalized to the whole body, nervousness very marked, exophthalmos was very apparent, Dallrymple, Graefe, Kocher symptoms were positive, muscular asthenia was intense. After several weeks of medical treatment the patient improved enough so as to be able to go through operation, which proved very successful.

Roeder, in 1920, observed 8 cases of toxic goiter and in 5 of them the hyperthyroidism had its onset definitely following influenza.

Farsano, in 1920, observed a patient with an acute thyroiditis producing chills, fever and pain. The patient showed the complete clinical picture of exophthalmic goiter. After incision with liberation of the pus, the thyroiditis and the thyrotoxic syndrome disappeared.

A great many other cases could be cited in order to prove this contention, namely, that there is a direct relation between the infectious process and the development of thyrotoxicosis. It shows, furthermore, that the organ primarily affected in all these cases is the *thyroid*. This



is of the utmost importance so far as the etiology of Graves's disease is concerned.

In cases similar to the ones just cited, where post mortems and histological examination of the gland could be performed, the microscopical changes found resembled very much those seen in thyrotoxicosis, namely, hyperemia, cellular hyperplasia, thinning of the colloid, leukocyte infiltration, etc., the only difference being that of degree. Furthermore, in the chapter devoted to thyroiditis, we have seen that chemical poisons such as phosphorus, nitrate of silver, iodine, turpentine, pilocarpine, may cause a toxic thyroiditis characterized by hyperplasia, degeneration, desquamation of the epithelial elements, thinning or absence of colloid, more or less marked hyperemia. The same is true in toxic thyroiditis caused by bacterial toxins. As we have seen in the chapter on Toxic Thyroiditis, Roger and Garnier, Crispino, Torri, De Quervain, and others found that the introduction of bacterial toxins into the thyroid circulation exerted upon the thyroid gland about the same influence as the chemical poisons: namely, hyperemia, proliferation and desquamation of the epithelium, diminution or absence of the colloid, etc. The same pathological findings are found to a certain extent in thyroid glands during acute infectious processes. A number of cases of toxic syphilitic thyroiditis with all the symptoms of an acute thyrotoxic goiter, exophthalmos included, have been reported in the secondary stage of syphilis. The lesions may not be such as to be macroscopically detectable; the microscope, however, shows that these typical lesions are present. For instance, Roger and Garnier, examining 40 thyroid glands taken from patients who had died of scarlet fever, diphtheria, acute gastro-enteritis, diffuse cerebrospinal meningitis, peritonitis, rabies, and smallpox, found in nearly every case marked histological changes in the thyroid. In some instances the epithelium had proliferated to such an extent as to form papillary formations projecting into the alveolar lumen. At the same time cellular desquamation was present, colloid was thin or absent, interstitial connective tissue showed little or no pathological changes except in the thyroids of patients who died from tuberculosis; there a diffuse sclerosis was found. Crispino, Sarbach, Serrafini, Vitry and Giraud came to the same conclusions. In 1888, Halsted found that hyperplasia of the thyroid of dogs occurred after injection of several cubic centimeters of bouillon culture of staphylococcus into the peritoneal cavity. The same was true when a mild form of peritonitis had been produced in these animals, a peritonitis, however, which was not rapidly fatal.

De Quervain, investigating the condition of the thyroid in 45 cases where the cause of death was tuberculosis, peritonitis, puerperal infections, diabetes, scarlet fever, smallpox, measles, diphtheria, typhoid,



pneumonia, found marked changes in the epithelium characterized by a proliferation, desquamation, fatty degeneration of the desquamated cells, thinning, diminution or absence of the colloid, and hyperemia of the whole gland. In certain cases he found interalveolar leukocytic infiltration. In patients who died from cancerous cachexia, diabetes, nephritis, Addison's disease and uremia, no pathological changes in the thyroid were found. Finally, Gregor, in 26 thyroids of children who died from scarlet fever, found the same pathological changes reported by all the other authors and Farrant not only observed thyroid hyperplasia occurring in many diseases, but also observed that diphtheria antitoxin produced constantly hyperplastic changes in the thyroids of horses and guinea-pigs.

### GRAVES'S DISEASE IS A TOXIC THYROIDITIS.

How shall we interpret all these facts? If we throw them all together, the first conclusion we come to is that the thyroid reacts in the same way to the most various and most diverse processes. For instance, in thyroiditis, be it bacterial or toxic, we find hyperemia, cellular hyperplasia, increased absorption of colloid, leukocyte infiltration, thyrotoxic symptoms. In iodine-Basedow, where iodine seems to be the provocative agent, causing very likely a toxic thyroiditis, we find, too, hyperemia, cellular hyperplasia, diminution and thinning of the colloid, leukocytic infiltration, thyrotoxic symptoms. In acute infectious processes of the organism such as typhoid, etc., the gland shows in a lesser degree, it is true, but nevertheless unmistakably, the same pathological and clinical signs. Although the causes vary, the results are the same. In iodine-Basedow as in toxic and bacterial thyroiditis, as in the ordinary Basedow, the nature of the histological changes and, to a certain extent, of the clinical symptoms, is the same. There is only a difference of degree. We are consequently warranted in concluding that in thyrotoxicosis the mechanism of the development of the disease is similar to the one which occurs in iodine-Basedow, and in thyroiditis, be it toxic or bacterial. In the latter conditions the process is acute, whereas, in Basedow it is chronic. Furthermore, as in iodine-Basedow and acute thyroiditis, the thyroid gland is involved first and the symptoms occur only after, had we here only that proof in favor of our contention, it would still be logical to conclude that in the great majority of cases of Basedow's disease, *the starting-point takes place in the thyroid*. Hence we disagree with Mikulicz who claimed that the thyroid acted as a "multiplier;" with Crile, who thinks that it plays the part of an "activator" inaugurated directly or indirectly by the nervous system.

If we carry our line of reasoning a little further, as in iodine-Basedow, in bacterial, toxic, or chemical thyroiditis, the true nature of the process is a *toxic one*, we shall naturally have to admit as a consequence of it that in the true Basedow disease we have to deal with a similar toxic process, too. In the last analysis the whole question resolves itself into a matter of a *toxico-infectious process*, in other words, Graves's disease is a *toxic thyroiditis*.

So understood, this theory will explain the pain to pressure so often seen in true thyrotoxic goiters; it will explain the adhesions so often found around the goiter at the time of the operation, even when no external treatment, as iodine or *x*-rays, has been used; it will explain why in exophthalmic goiter the cervical lymph nodes are hyperplastic, why there is a leukocytic infiltration throughout the thyroid parenchyma; and it will explain, partly at least, the slight rise in temperature sometimes seen in Graves's disease. It is not necessary to look for a *specific thyrotoxic microbe* in order to explain all these clinical findings; they may be caused by all the microbes, their toxins, the products of auto-intoxication, or any toxic chemical agent. Under the spur of their irritation the thyroid works at top speed; in order to increase its efficiency and in order to suffice for its tasks, be it to neutralize or to eliminate these poisons, or whatever it may be, it increases its blood supply; it undergoes hyperplasia.

This theory consequently leads us to consider the histological changes seen in the thyrotoxic thyroid as the result of *hyperfunction*. Hence the theory of *hyperthyroidism*. Everything tends to prove it, especially the increased blood supply. Furthermore, Askanazy, Müller and Farmer found that the lymphatic veins and connective tissue in Basedow's disease were filled with colloid, whence they concluded that this disease was caused by an exaggerated amount of colloid reaching the blood.

As a result of the increased function of the thyroid there is constantly in the blood an increased amount of thyroxin which, as we know, acts electively upon the central and vegetative nervous systems. Thus a constant and abnormal stimulation is being kept upon the thyroid by the nervous system which in turn stimulates the thyroid. Hence the establishment of a vicious circle: as we have said before, the thyroid drives the nervous system and the nervous system drives the thyroid.

This increased, and possibly modified, thyroid secretion through its lipoids acts electively upon predisposed organs already sensitized by sympatheticotrope, vagotrope, cardiotope, ovariotrope, etc., substances. Sensitization may not necessarily have been done previously by the thyroid: the polyglandular, the nervous system, etc., may have done it.

This theory seems to me to answer most satisfactorily many questions. Thus, the protean origin of Graves's disease is no more a puzzle;

the remote causes of it are indeed numerous and diverse, as infectious diseases, disturbed polyglandular function, chemical agents, etc., but the immediate cause is always the same: the *hyperfunction of the thyroid*. Thus, we shall understand better why Graves's disease is more prevalent at the time of puberty and menopause. Indeed, besides the disturbed nervous equilibrium, and possibly just because of it, besides the part which the organs of internal secretion play, toxic products due to the disturbed metabolism circulate in the blood and become injurious to the thyroid, hence toxic thyroiditis and hyperfunction. Even in cases where the primary lesion lies in the nervous system, as in cases of shock, fright, etc., the theory still holds good. Indeed, in such cases it is reasonable to admit that besides the direct influence from the nervous system upon the thyroid, products of refuse due to a suddenly increased and disturbed metabolism as shown by sweating, diarrhea, vomiting, disturbed renal function, etc., which accompany shock are driven into the circulation and may prove injurious to the thyroid and incite it to overfunction. At least these injurious stimuli may be sufficient to start a vicious circle between the thyroid and the nervous system; when once started there is no reason for stopping. Both links, however, namely, the thyroid and the nervous system, are necessary for the production of the disease: let us not forget that the section of the restiform bodies causes exophthalmic goiter as long as the thyroid is present; if it has been removed previously, the syndrome does not take place.

**Dysthyroidism.**—There is some evidence showing that the secretion of the thyroid is not affected quantitatively only but qualitatively also: in other words, besides *hyperthyroidism* we have *dysthyroidism*. This conclusion is based upon Marinesco's experiment. He demonstrated that the antigen from a Basedow struma, when mixed with serum taken from thyrotoxic patients, prevents hemolysis on account of the formation of antibodies. If, however, the antigen has been taken from a normal thyroid gland then hemolysis takes place: hence the conclusion that the colloidal nature of the thyroid secretion is changed qualitatively. Klose is an enthusiastic believer in the dysthyroidism theory. According to him, in ordinary conditions the iodine is fixed by the thyroid to some albuminous substance in order to form the thyroglobulin. In pathological conditions, however, the metabolism of iodine does not take place properly. Klose admits then the existence of a hypothetical substance which he calls "Basedow-iodine," very toxic, closely resembling the inorganic iodine, and exerting vagotrope, sympatheticotrope, cardiotrope, ovariotope influences, thus determining the thyrotoxic syndrome.

This theory would, of course, help us to understand why it is not necessary to have a great deal of hypersecretion of the thyroid if that secretion is vitiated. That would explain the cases where little

or no histological thyroid changes are present, as the latter are mostly evidencing hyperfunction. Of course, what part the hyperthyroidism and the dysthyroidism play in the production of the thyrotoxic syndrome is an open question.

**Colloidal Point of View.**—The fact that in simple goiter the alveoli contain a thick colloid, and in thyrotoxic goiter the colloid content is thin or absent, from the colloidal chemistry standpoint, means only that in the first case we have to deal with a “gel” and in the second case with a “sol” condition. The “dispersion’s condition” of iod-colloid is entirely different in both conditions. In the first case it is diminished, hence, the thick colloid-gel. In the second case, it is exaggerated, hence, the thin colloid-sol. The thin colloid-sol is, of course, much more easily mobilized than the thick colloid-gel. Hence, its rapid dissemination into the system through the lymphatics. Kottmann has shown with his photo-chemical method that the dispersion’s power of iodide-silver is considerably increased when iodine is administered, thus confirming the view that iodine converts the colloid-gel into a colloid-sol, in which case the “dispersion condition” of iod-colloid is considerably increased. He has shown, too, that calcium lactate, sodium phosphate have the opposite effect. They transform the colloid-sol into colloid-gel. This means that in thyrotoxicosis the iod-colloid is in an increased condition of dispersion and that it is able to flood the body on account of its sol condition.

When iodine is administered, it is taken up by the thyroid and converted into iod-colloid. The degree of dispersion of this iod-colloid will determine if we shall have an iod-colloid-sol, or an iod-colloid-gel. Most likely the same process takes place in a toxic thyroiditis following acute infections, nervous shock, etc.

We may assume that the chemical properties of the colloid-sol are different from those of the colloid-gel, just as the starch-sol is different from the starch-gel; the first gives the iodine reaction, the second does not.

**Part of the Thyrotoxic Symptoms May Be of Anaphylactic Origin.**—It is more than probable that part of the thyrotoxic symptoms observed are phenomena of “anaphylaxis” due to the absorption into the circulation of abnormal albuminous thyroid products. The intense itching of the skin without eruptions resembles closely the itching observed in anaphylaxis. Indeed, the thyrotoxic thyroid albuminous substances may very well be enough modified so as to act as a foreign albumin, thus “anaphylactizing” the organism and producing toxins centering their effects upon the nervous system. This view is based upon Schittenhelm’s researches, which show that the substances resulting from the splitting of albumins into secondary products, produce an intoxication similar to the one obtained with peptones and characterized by fall of blood-



pressure, on account of peripheral dilatation, leukopenia, acceleration of the lymphatic current, increased glandular secretion, etc. In short, according to Biedl and Krauss, this toxic syndrome resembles closely the one of anaphylaxis and of Basedow's disease. These views are further strengthened by J. W. Jobling and W. Petersen, who showed that iodine incubated with blood serum lowers markedly its antiferment property; the serum of these patients treated with iodine becomes-toxic because of autolysis of the glandular components; a similar process (absorption of the antiferment by agar, kaolin, bacteria, etc.) being the basis of the toxicity of the so-called anaphylatoxin.

**Why is it that Some People Have Exophthalmic Goiter and Others Do Not?**—Why is it that some people will stand large amounts of iodine while others cannot? Why is it that acute infectious processes will cause the thyrotoxic syndrome in some patients and not in others? Why is it that a shock, a fright which will not faze this one, will cause Graves's disease in that one? In answer to these questions, I will say: Why is it that between two men falling into a river, one will get pneumonia and the other articular rheumatism? Why is it that the liver, and the pancreas of certain individuals are able to take care of enormous quantities of carbohydrates without giving rise to glycosuria, whereas in others they are unable to do so? Why is it that mercury will cause an acute nephritis in some individuals and an acute enteritis in others, and no symptoms in a great number of others? Most likely because the injury settles in the *locus minoris resistentiæ*. The same is true for the thyroid. There must be conditions unknown to us, but nevertheless existing, which must render certain thyroids more susceptible to injurious stimuli than others, just as certain special conditions must intervene to inhibit the hepatic and pancreatic function in the metabolism of carbohydrates, or to render certain kidneys and intestines susceptible to mercury, just as certain requirements have to be met to allow the tubercle bacilli to produce tuberculosis. Congenital weakness, heredity, abnormal disposition, abnormal susceptibility, disturbed nervous equilibrium, unsettled polyglandular system, all play their contributing part. When the truth is known, then very likely some reduced factor of safety, some chemico-biological disturbances or congenital predisposition, will appear as the cause or the determining causes. As we have already said, "Nature does not know a cause but causes."

**Summary of Conclusions Concerning the Etiology of Graves's Disease.**—Graves's disease is a thyro-neuro-polyglandular disease. The thyroid is almost always primarily affected; however, very much less frequently the nervous system can be the primary cause, too. There exists between them a mutual interaction; the thyroid drives the nervous system and the nervous system drives the thyroid: this constitutes a vicious circle

which can be broken by medical or surgical treatment. From a pathological and clinical standpoint, Graves's disease resembles in every respect what we see in acute thyroiditis, be it toxic or bacterial, and what we see in iodine-Basedow which is, too, a toxic thyroiditis. Hence we feel warranted in concluding that *Graves's disease is a form of toxic thyroiditis*. It is caused by any infectious disease, by any toxic condition arising from a disturbed polyglandular function, by a disturbed nervous equilibrium, by a disturbed metabolism etc. Under such conditions the thyroid secretion is quantitatively and possibly qualitatively affected, and becomes the cause of the pathological syndrome. The symptoms observed in Graves's disease are due to hyperthyroidism, to disturbances of the nervous and polyglandular systems, and probably some are due to anaphylaxis. The exact chemical reaction which takes place in order to bring about the whole syndrome is still a matter of speculation. It is most likely due to a disturbed condition of dispersion of the iod-colloid in the blood.

## CHAPTER XXXVIII.

### THE TREATMENT OF GRAVES'S DISEASE.

WE have now reached the crucial part of our work. The most elaborate researches, the most beautiful theories, the greatest effort and expenditure of energy will fall short if they do not directly or indirectly resolve themselves into some advancement of the therapeutic end, the final test of every scientific effort. From the conception one makes of the nature and etiology of this disease will derive the line of treatment. Internists who regard Graves's disease as a neurosis or as a disturbance of central origin, or as a peculiar and enigmatic trouble of some sort, no matter where it has its seat, *provided it is not in the thyroid gland*, still work in the dark, hence the great, motley mixture of what is called "medical treatment." Surgeons, on the other hand, who consider the thyroid as the "guilty factor," will experience no hesitancy; their road is open; "Heraus mit dem," Out with it! A radical and not the ideal means most assuredly, but the best we have at hand so far, and the most fertile in results. We all admit that it would, of course, be more elegant, more artistic, to be able to resort to some "specific agent" which, injected subcutaneously, intravenously, or taken by mouth, would bring about a sure cure. It would be an art of the highest type to be able to say to the patient as Christ said to the lame man, "Arise, take up thy bed, and walk." Unfortunately, we are only men and not gods, we think and act according to our own little intelligence and limitations. As yet the truly "specific agent" has not been found. That it will some day there is no doubt in my mind. To find it will be the glorious task of *biological chemistry*.

Quite a marked step forward in this direction has been taken just recently. By delicate, chemical manipulations, Iscovesco was able to isolate from the various organs of internal secretion, *lipoids*, many of them possessing decided physiological properties. Lipoids are contained in all the organs of the body. Some of them have an antagonistic, others a synergetic action. A given organ contains numerous lipoids. In the thyroid, for instance, there are several lipoids, each one possessing seemingly entirely different properties. One of the lipoids injected into young animals produces myxedematous symptoms; another produces thyrotoxic symptoms, another causes a congestion and hypertrophy of the gland itself. The ovary contains a lipoid influencing the ovary itself,

another influencing the uterus and its appendages, and another influencing the thyroid. The lipoids which influence other organs are called *heterostimulants*; the lipoids which influence organs from which they are derived are called *homostimulants* or *self-activating*. These facts, if confirmed, will not only solve many obscure problems, but will also widen considerably our field of therapeutic action. The isolation of these different substances and their appropriate use will be of tremendous value to the future physician. For the time being, however, we must content ourselves with what we have at hand, "medical" and "surgical," and try to make the best of it.

If the shades of Flajani, Graves or Basedow could come back into the world, they would certainly be greatly shocked to see that the disease which bears their names has slipped out of the bosom of internal medicine into that of surgery. Very likely they would turn and with inquisitive and reproaching tone interview the internist, and as in the "Parable of the Talents," they would say, "What have you done with our legacy?"

It is certainly not through mere fancy that the surgeon has become entranced with the thyroid question in Graves's disease. For long years it looked as if Basedow's disease would remain forever a medical disease. So long as the nervous symptoms, tachycardia, and exophthalmos were given the most prominence in the clinical syndrome, and so long as the goiter was considered only as a secondary and unimportant factor, the disease seemed to remain forever the appanage of the internist, and "a noli me tangere" for the surgeon. As years went by, however, with no progress made in curbing the disease, and with no new conceptions of its etiology, the disease was languishing in the painful marasmus of the "rest cure."

At a time when internal medicine had seemingly disinterested itself in this question, two great men, internists themselves, Gauthier de Charolles and Moebius, came along and with a new theory gave a powerful impetus to the question. It is true that previous to them a few operations had been performed for exophthalmic goiter by Kocher and others. These operations were intended, however, to remove Basedowified goiters causing mechanical symptoms. Great had been the surprise of everyone to see that at the same time the functional disturbances were relieved also. Hence suspicion became aroused, new but still undecided etiological conceptions, which, as just said, were soon shaped into a definite form by Gauthier and Moebius. In their judgment the disease no longer took its origin in some nervous, circulatory, or other problematic disturbances. It was no longer a neurosis. In their judgment the goiter, which for so long had been considered as unimportant, was now the responsible factor; in fact, it was the *primary cause* of all the trouble. That day Graves's disease became at once a surgical disease; from the



sanitaria and rest cure places it jumped into the operating rooms. From that time on it ceased to live in the marasmus in which it had been before. It became a burning question taken up at once all over the world. Since surgery has adopted as one of its own, this abandoned child of internal medicine, it is only just to say that so far as pathology and treatment are concerned, great progress has been made. It is to surgery that we owe most of what we know today of Graves's disease, just as it is to surgery that we owe most of what we know of appendicitis, gastric and duodenal ulcer, gall-bladder diseases, etc.

**Is There Truly a Medical Treatment for Graves's Disease?**—If by that we mean a well-defined, classical, efficient, specific, therapeutic line of conduct to be followed in such cases, then *there is none*. Indeed, there can be no doubt of that. If, on the other hand, by "medical treatment" we mean anything which is not surgical, we must concede that there is such a thing. With this form of treatment everyone feels at liberty to "experiment" with whatever he sees fit, hence the multitude of medical means employed, as for instance iodine, arsenic, iodides of all kinds, bromides, digitalis, belladonna, atropine, ergotine, ether, veratrum, strophanthus, quinine, nux vomica, phosphate of soda, convallaria majalis, etc.; faradization, galvanization, currents of high frequency, hydrotherapy of all sorts; sojourn at the sea or in high altitudes; gymnastics with Zander's apparatus; mountain climbing, etc.; all imaginable diets, etc., some authors advising forced feeding, others, the hunger cure; some advising forced drinking, others the thirst cure; as mineral waters of all sorts, and kephir, milk, zoulac; as serum, blood or milk of thyroidectomized animals, thyrotoxic serums; as finally, extracts of the glands of internal secretion, as adrenals, pancreas, hypophysis, ovarian extracts, thymus, testicles, etc.

Everyone will admit that this medical therapeutic gamut is most variant, and everyone according to his taste can make his choice. But please do not think for one moment that I am trying to ridicule the medical treatment. I know too well that each one of these means employed has to its credit some improvements and some cures, and as everyone knows, too, that some patients get well without any treatment, and as was said by Mayo, some get well in spite of any treatment. Too often we hear adversaries of surgical treatment boast that they have cured thyrotoxic patients with the rest cure, with milk diet, with Forcheimer treatment, and what not. We all can pick out of our series, medical as well as surgical, some brilliant results in order to support our contention. That is not the point. We know that this is true. But the point is: Of the total number of Basedow patients treated medically or surgically, what numbers improve or get well, and what is the death-rate? That can be best answered by statistics. As Riedl has said, "Medicine,

like theology, has its dogmata." When once established, it is difficult to eradicate them even when wrong. The danger of surgical treatment in Basedow's disease is one of these dogmata; its inefficacy is another. Let us see what we can gather from statistics.

**Results of Medical Treatment.**—Williams, out of 1569 surgical cases showed a mortality of 4 per cent, a cure of 72 per cent, while 300 medical cases treated with the antiserum gave 20 per cent cure, 60 per cent improvement, 10 per cent no effect, and 10 per cent death. Baruch, comparing the results obtained by operation and medical treatment, found for the cases treated medically: 0 per cent of cure, 5.2 per cent were able to resume their full work, 26.3 per cent were only partially able to resume their work, 68 per cent were unable to work at all, whereas the surgical treatment allowed 17.9 per cent to resume their full work, 51 per cent to resume their partial work. He furthermore found that with medical treatment cardiac hypertrophy never diminished, whereas it disappeared in 70 per cent of the operated cases. In non-operated cases he found, further, that exophthalmos remained unaffected in 7.6 per cent, was improved in 69.2 per cent, and got worse in 23 per cent, while in cases treated surgically, exophthalmos disappeared in 39.6 per cent, was improved in 54.5 per cent, and remained unaffected in only 3.2 per cent. He reported, too, that tremor disappeared in 77 per cent of the operated cases and never in the ones treated medically. White found that in 108 cases treated medically by him, 21 died, 61 were cured, 21 improved, and 5 remained unaffected. The mortality with medical treatment is high; 10 per cent for Cheadle and Thompson, 12 per cent for Von Graefe, Von Dusch and Buschan. These figures are based upon 900 cases. Charcot, Williamson, and Stern's death-rate is 25 per cent. Ord and Mackenzie, out of 55 cases, obtained 10 complete cures, 24 improvements, 4 negative results, and 14 deaths. Murray had 7 deaths out of 40 cases. Vetlesen, out of 34 cases, had 7 cures, 20 improvements and 7 deaths. Frankl-Hochwart out of 60 cases found 25 fruste forms which remained unaffected by treatment; out of the other 35 cases of true Basedow, 9 cures, 11 negatives, and 15 deaths. Lichty had 3 deaths out of 74 cases. Sainton was able to collect 219 cases treated by serotherapy; 10 per cent were cured, 80 per cent improved, 8 per cent were failures, and 2 per cent exacerbations. Rogers and Beebe, in 1909, out of 480 cases gave 15 per cent of cure objectively, 10 per cent cured subjectively, 15 per cent ameliorated, and 17 per cent failures. In 1915 Beebe, without furnishing any statistics, estimated roughly that he had treated 3000 patients with antiserum with 50 per cent cure, 30 per cent improvement and 20 per cent failure. We must not forget, however, that this author in a general way seems to be very sanguine in his conclusions, as shown by his recent "cancer cure." In 1910 Kocher reported

1000 cases treated surgically and 100 cases treated medically. The mortality of the operated thyrotoxic cases amounted to 4.83 per cent, while the cures gave 80 per cent. From the 100 cases treated medically, 22 had to be operated because of the failure of the medical treatment to bring about a cure, or at least, encouraging improvement. From the remaining cases, 18 per cent. were cured, 27 per cent. improved, 33 per cent remained unaffected, and 22 per cent died. Syllaba reports 51 cases of Graves's disease treated medically; 9 died, 4 were failures, 27 ameliorated, improved, or cured. The balance of the other cases is not given. W. H. Becker went over all the cases admitted into the clinic of Prof. Dr. Voit in Giessen from 1890 to 1912. During that period of time, 40,941 patients were admitted. Among them were 70 cases of Basedow's disease. As some of these patients were readmitted at various intervals the true total number of patients amounted to 61. Out of these 61 cases the records of the clinic show that only 1 patient was discharged cured. From the remaining 60 cases, 36 were discharged as improved (60 per cent), 21 were unimproved (35 per cent), 1 case was sent over to the surgical clinic, and operated, then returned to the medical clinic for further treatment with galvanization of the sympathetic and thymic opotherapy, and only then dismissed as improved. From the 2 remaining cases nothing could be ascertained, as no history was to be found. The treatment used from 1890 to 1903 was a purely symptomatic one: arsenic, bromides, rest in bed, ice-cap for the heart, while occasionally iron and baldrian, and galvanization of the sympathetic were employed. In 1903 for the first time the antithyroidine of Moebius was used five times with 4 improvements and 1 negative result. Rhodagen was used twice with 1 improvement and in the other with only a slight improvement. In 1906, x-rays were employed in 1 case which had been treated without success with antithyroidine of Moebius. In 1907 a meat-free diet was tried on 5 patients; 4 were improved, 1 showed only very slight temporary improvement, 1 remained negative. Four times Voit used phosphate of soda and phytin treatment; 3 were negative, 1 improved and 1 markedly improved. Becker went to the trouble to look up what had become of these last 10 cases since 1907. He succeeded in getting in touch with only 7 of them. In all the improvement had remained the same. They were more or less materially improved but not cured.

As reported by A. Stenzel, in 1912, 54 cases of Basedow's disease were observed in Stintzing's clinic at Jena. Otto says 10 of these were severe cases, 30 moderately severe, and 14 were of the milder type. Of these 70 per cent were women and 30 per cent men. These cases were treated medically, according to the newer procedures, for at least six weeks. If at the end of this time the patients did not show improvement, they were transferred for surgical treatment. Eight of these cases, or

about 15 per cent, were able to resume their work after treatment for an average period of two months. Of these 8 cases, 7 were mild and 1 moderately severe. In all, however, there was a typical Basedow complex, the cardinal symptoms all being frankly present. Twenty-one cases, or about 39 per cent, were improved—2 of these being mild forms, 15 moderately severe, and 4 severe. Nineteen cases, about one-third of the whole number, resisted all medical treatment. Among these were 3 mild cases, 12 moderately severe cases and 4 of the severe type.

MEDICAL CASES.

Name.	No. of cases.	Cure, per cent.	Improvement, per cent.	Rate per cent. Negative results, per cent.	Death, per cent.
Williams . . . .	300	20.0	60.0	10.0	10.0
Baruch . . . .	...	..	<div> <div>31.5</div> <div>5.2</div> <div>able to work</div> <div>26.3</div> <div>partially able</div> </div>	68.0	
White . . . .	108	56.4	19.4	4.6	19.4
Cheadle . . . .	not given	..	...	..	10.0
Thompson . . . .	not given	..	...	..	10.0
Von Graefe . . . .	not given	..	...	..	12.0
Von Dusch . . . .	not given	..	...	..	12.0
Buschan . . . .	not given	..	...	..	12.0
Charcot and Williamson . . . .	...	..	...	..	25.0
Ord and Mackenzie	56	17.85	42.89	7.14	25.0
Murray . . . .	40	17.5			
Vetlesen . . . .	34	20.58	58.5	..	20.58
Frankl-Hochwart .	60	25.0			
		fruste forms unaffected	—41.66		
remaining . . . .	35	25.71	...	31.42	42.85
Lichty . . . .	74	..	...	..	4.0
Sainton . . . .	219	10.0	80.0	8.0	0
Rogers					
Beebe . . . .	480	<div> <div>15.0</div> <div>objective</div> <div>10.0</div> <div>subjective</div> </div>	15.0	17.0	0
Kocher . . . .	100	..	...	22.0	0
	78	18.0	27.0	33.0	22.0
Syllaba . . . .	51	..	52.94	7.84	17.64
Voit-Becker . . . .	61	1.65			
remaining . . . .	60	..	60.0	35.0	0
Otto . . . .	54	15.0	39.0	35.0	
Williams . . . .	23	..	31.8	..	25.0

In general, this material showed that not only cases of lighter grade, but also of severer types, were not amenable to medical treatment. In



the cases in which antithyroidine (Moebius) was used, no good results were observed. This was true also of the  $x$ -rays, where used. In a large number of those cases in which medical treatment had failed, the symptoms disappeared after operation.

**Conclusions.**—How eloquent all these figures are! Do they not show that one thing must strike us forcibly, namely, that medical statistics are utterly insufficient? It is true that once in a while internists will report one or two cases treated successfully with medical means, but large statistics describing *in extenso* their cases, their immediate and remote results, are rare. Let us hope that internists will in the future strive to set forth more and better data. The little there is of these, however, does not well stand comparison with surgical statistics. From them it appears that medical treatment is far less efficient, far less rapid in results, far less fertile in cures and improvements, and far more dangerous *quoad vitam*. As time goes by the surgical death-rate is being constantly reduced. So long, however, as we shall have to revert to surgical means to cure thyrotoxicosis, so long as we cannot disregard the heart of the patient, his nervous system, his thymus, his chromaffin system, his liver, his kidneys, there will always be an “unavoidable death-rate.”

It is remarkable to see how operative success improves with the increased experience of the surgeon. For instance:

## KOCHER'S CASES.

Year.	Case.	Death rate, per cent.
1902	59	6.5
1906	167	5.0
1910	376	4.0
1911	167	2.3
1912	130	1.5
1916	300	1.0

## MAYO'S CASES.

1904	40	15.0
1907	110	8.0
1909	405	4.5
1911	1000	3.7
1912	276	0

## CRILE'S CASES.

First	1169	16.0
1921	315	1.8

## SURGICAL CASES.

Dates and names.		Cases.	Cures. Per cent.	Great improvement. Per cent.	Moderate improvement. Per cent.	Negative results. Per cent.	Death- rate. Per cent.	Remarks.
1894	Buschan . . . . .	80	38.75	25.0	....	27.5	7.5	In 25 cases results unknown.
1894	Herzkind . . . . .	40	42.5	42.5	....	7.5	7.5	
1895	Mikulicz . . . . .	11	54.5	45.4	....	....	....	
1896	Kinnicutt . . . . .	187	40.1	33.15	....	5.87	6.95	
1896	Mattieson . . . . .	117	44.4	23.08	....	20.5	5.98	
1896	Starr . . . . .	190	38.9	23.68	....	1.57	12.1	I relapse.
1896	Lemke . . . . .	17	....	100.0	....	....	....	
1896	Riedel . . . . .	11	36.3	18.1	....	45.4	....	
1896	Schulz . . . . .	20	90.0	....	....	5.0	5.0	
1897	Kümmel . . . . .	16	75.0	12.5	....	....	....	
1898	Wormser . . . . .	204	....	100.0	....	....	....	I unknown.
1898	J. Wolf . . . . .	9	66.5	....	....	11.1	11.1	
1899	Rehn . . . . .	319	53.29	28.52	....	4.38	13.79	
1900	Wittmer . . . . .	23	40.9	36.2	9.2	9.2	9.2	
1900	Reinbach . . . . .	18	66.5	22.5	....	5.5	5.5	
1900	Schulz . . . . .	20	90.0	....	....	5.0	5.0	9 of the cures still lasting 4 to 9 years after operation.
1900	Mikulicz (Reinbach) . . . . .	18	66.66	....	22.2	5.5	5.5	
1900	Krönlein (B. Wittmer) . . . . .	23	39.13	26.08	8.69	13.04	13.04	
1901	Ehrlich . . . . .	9	....	100.0	....	....	....	Cures lasting 9 years and more.
1901	Kümmel (Schulz) . . . . .	20	70.0	10.0	15.0	....	....	
1902	Kocher . . . . .	59	76.27	13.55	3.38	....	6.77	
1902	Kocher . . . . .	93	75.26	18.27	....	....	6.45	
1903	Curtis . . . . .	11	60.0	10.0	....	....	30.0	
1904	Mayo . . . . .	40	67.5	17.5	....	....	15.0	Reporting operations from 1883-1899.
1905	Friedlein . . . . .	20	70.0	....	....	3.0	....	
1905	Hartley . . . . .	15	100.0	....	....	....	....	
1905	Lessing . . . . .	8	50.0	25.0	....	....	25.0	
1906	Brugsch . . . . .	72	70.83	29.13	....	....	....	
1906	Kocher . . . . .	167	72.45	13.17	....	....	3.53	8 cases not followed.
1906	Shepherd . . . . .	17	52.94	17.64	....	5.87	23.5	

1906	Rudd (Schulz)	.	.	.	.	50	74.0	14.0	....	2.0	12.0	
1907	Kocher	.	.	.	.	283	73.8	19.0	....	....	3.4	6 cases unknown.
1907	Berg and Ackerman (Landström)	.	.	.	.	54	37.03	....	12.96	20.37	11.1	
1907	Doyen	.	.	.	.	10	100.0	....	....	....	....	11 cases unknown.
1907	Garré (Moses)	.	.	.	.	35	11.42	28.54	17.14	8.54	2.85	
1907	Izina (Mat. of Hildebrandt)	.	.	.	.	7	85.5	....	....	14.3	....	3 cases unknown. Cures lasting
1908	MacCash	.	.	.	.	23	17.39	52.17	8.79	4.34	4.34	4, 7, 8, 12 years after operation.
1908	Klemm	.	.	.	.	32	78.125	3.125	....	3.125	....	
1908	Dunhill	.	.	.	.	32	75.0	....	....	3.125	....	7 cases unknown.
1908	Bier (Krueger)	.	.	.	.	11	27.27	45.45	9.0	9.0	9.0	
1908	Th. Kocher	.	.	.	.	153	....	98.7	....	....	1.3	
1909	Mayo (McWilliams)	.	.	.	.	167	70.0	18.56	5.98	5.32	....	
1909	Beek	.	.	.	.	50	90.0	6.0	....	4.0	....	
1909	Judd and Pemberton	.	.	.	.	176	....	....	....	....	7.0	
1909	Krecke	.	.	.	.	17	70.58	....	23.53	....	5.88	
1909	Hänel	.	.	.	.	21	38.1	42.8	....	....	....	
1910	J. Broekaert	.	.	.	.	11	100.0	....	....	....	....	
1910	Kocher	.	.	.	.	376	76.0	....	....	....	3.9	
1910	Von Eiselsberg	.	.	.	.	44	61.4	34.1	....	40.0	....	
1911	Enderlen	.	.	.	.	40	70.0	20.0	....	2.2	2.2	
1911	Mayo	.	.	.	.	1000	70.0	26.3	....	....	3.7	
1911	Sudeok	.	.	.	.	26	84.6	4.0	....	....	4.0	
1911	Rehn	.	.	.	.	61	67.21	98.3	....	1.63	1.31	
1911	Harris	.	.	.	.	29	....	....	....	....	6.89	
1911	Schugan	.	.	.	.	42	1.42	4.04	....	4.04	2.38	
1911	Bartlett	.	.	.	.	45	....	....	....	....	4.44	
1911	Terry	.	.	.	.	41	....	....	....	....	2.43	
1911	Rixford	.	.	.	.	23	....	....	....	....	....	
1911	Tinker	.	.	.	.	167	....	....	....	....	....	
1911	Alamartine and Perrin	.	.	.	.	120	70.8	22.0	....	7.2	....	
							(operated over 3 years)					
1911	Kocher	.	.	.	.	167	....	....	....	....	2.3	
1912	Klosé	.	.	.	.	61	75.5	9.8	....	1.6	13.1	
1912	Dunhill	.	.	.	.	230	....	....	....	....	1.73	
1912	A. Kocher	.	.	.	.	130	98.4	....	....	....	1.53	
1912	A. Kocher	.	.	.	.	360	44.4	41.38	7.77	....	....	22 died since from intercurrent diseases.
							(Reporting remote results in advanced and acute cases)					
1912	Mayo	.	.	.	.	276	....	....	....	....	....	Cases from Chicago surgeons.
1912	Fuller	.	.	.	.	600	....	....	....	....	5.0	

## SURGICAL CASES—Continued.

Dates and names.	Cases.	Cures, Per cent.	Great improvement, Per cent.	Moderate improvement, Per cent.	Negative results, Per cent.	Death- rate, Per cent.	Remarks.
1913 Klosé . . . . .	1216 (taken from literature 1896-1912)	61.8	21.8	3.1	5.0	7.6	
1914 Glaserfeld . . . . .	534 (cases taken from literature)	63.8	12.7	7.6	5.8	4.6	
1914 Otto Klinke . . . . .	6825 (operations taken from literature)	17.6	68.1	....	38.8	32.9	
1914 W. S. Halsted . . . . .	500	60.0	25.0	....	....	....	
1914 Frazier . . . . .	37	40.5	43.2	16.2	....	....	
1914 Rogers . . . . .	208	78.0	20.1	....	....	1.9	In his end-results Frazier claims 90 per cent. of cures.
1914 Rogers . . . . .	ligations 1-3 vessels 36	78.0	....	....	....	0	
1915 Frazier . . . . .	ligations 4 vessels 80	....	....	....	....	11.76	
1915 Frazier . . . . .	17 ligations	....	....	....	....	....	
1915 A. Stark . . . . .	69	30.0	40.0	....	21.0	9.0	
1916 André Crotti . . . . .	122	....	....	....	....	3.2	
1916 Miles F. Porter . . . . .	100	100.0	....	....	....	....	
1916 Vernon C. David . . . . .	200	....	....	....	....	5.5	
1916 Vernon C. David . . . . .	6	50.0	50.0	....	....	....	
1916 Vernon C. David . . . . .	35	47.3	31.0	15.0	5.0	....	These were moderate cases. These were marked cases These were severe cases These cases were collected from American surgeons.
1916 Vernon C. David . . . . .	19	31.4	40.0	23.0	6.0	....	
1916 Chas. H. Frazier . . . . .	1415	....	....	....	....	3.5	
1916 Judd and Pemberton . . . . .	121	45.4	23.9	4.1	6.6	....	
1916 André Crotti . . . . .	100	....	....	....	....	3.2	
1917 André Crotti . . . . .	137	....	....	....	....	0	
1918 Sloan . . . . .	398	....	....	....	....	3.8	
1918 Frazier . . . . .	?	....	....	....	....	3.5	
1918 Ochsner, Judd, Porter and David . . . . .	1415	....	....	....	....	3.5	
1918 Terry . . . . .	420	....	....	....	....	3.2	
1918 J. Rogers . . . . .	296 ligations 1-4	79.0	15.0	....	6.0	3.0	
1920 Crile . . . . .	351	....	....	....	....	1.1	
1922 Crotti . . . . .	500	....	....	....	....	1.6	



Riedl had 40 per cent in his first 40 cases, 3.3 per cent in his following 30 cases. The writer had 8 per cent deaths in his first series of 100 cases, 7 per cent in his second series of 122 cases, and 3.2 per cent in the following series of 100 cases, and no deaths in the series of 137 cases. Crile had 31.3 per cent deaths in 16 cases, 10 per cent in the following 30, and 1.3 per cent in the following 150 cases. This progressive improvement in the death-rate is not so much dependent upon the improvement in technic of the surgeon, as upon the increased experience and knowledge of the disease, upon the more judicious selection of cases, and upon a better comprehension of the indications for operation in each given case. The surgeon learns by experience that Basedow patients are fragile, that they have no, or little resistance, that operations must be proportioned to their strength, and that failure to estimate the proper amount of surgical traumatism which the patient can stand may mean death.

**When Shall We Consider a Patient as Cured?**—If we glance over the statistics, either medical or surgical, we are struck by the fact that authors have a different way of appreciating the word *cure*. It is obvious that some regard as cured, patients who are regarded by others as only improved, and *vice versa*. What then shall we understand by *cure*? If by cure we mean the complete disappearance of objective as well as subjective symptoms, in other words, if we have in view a complete *restitutio ad integrum* cure in Graves's disease is less frequent than is admitted, be it in surgical or in medical cases. The degree of cure will be directly proportionate to the stage of the disease in which treatment is undertaken. Only in the early stage can surgical treatment give 95 per cent or even 100 per cent of subjective as well as objective cures. When once the disease has progressed beyond certain limits, when it has lasted for a long period of time, or when the organs have become anatomically damaged, the patient may feel subjectively cured; he may be able to resume his normal activity, yet there still remain some objective symptoms, as possibly some enlargement of the thyroid, some glaring look, some widening of the palpebral fissure, possibly some tremor, or some occasional tachycardia—all stigmata of the past pathological process, similar in some respects to the scars left by smallpox. In some instances we shall find that exophthalmos still remains in a more or less marked degree, yet the patient is cured. The reason is found in the fact that because the globus oculi has been pushed out of place for so long a time, production of retrobulbar connective tissue and fat has taken place, thus preventing the eye from sinking back into its former position. Exophthalmos in that case is no longer a thyrotoxic symptom, but has become an acquired condition. The patient may therefore be regarded as cured. In other instances some degree of

tachycardia or of myocarditis still remains, yet the patient is unconscious of it, he is putting on flesh and feels well. There, too, the cardiac symptoms are no longer thyrotoxic symptoms, but must be regarded as an acquired pathological condition. In short, the disease has subsided, yet indelible traces of it still remain. These patients are cured just as those who are burned are cured; the active process is extinguished, but there still remains the "scar," which in a more or less marked degree, according to its extent and seat, will add to the depreciation of these individuals. They are cured only so far, but the anatomical damages done to the organs remain.

It is to be desired that this word, *cure*, applied to Graves's disease, for the sake of clearness and discussion, be standardized. It might be well to classify our results in the following manner:

1. Complete cure.
2. Subjective cure.
3. Great improvement.
4. Moderate improvement.
5. Failures.
6. Made worse.

1. *Completely cured* are the ones in whom *restitutio ad integrum* has taken place. No objective or subjective symptoms remain as a living witness of the past pathological process. The patient has regained his former health.

2. *Subjectively cured* are those who subjectively feel well, are able to resume their normal activities, and are able to stand, emotional as well as physical, strain without undue reaction. There may be, of course, some occasional tachycardia, some occasional nervousness, some occasional tremor; they may still show some thyroid hyperplasia, some moderate degree of exophthalmos, some widening of the palpebral fissure, etc. These symptoms, however, are not sufficiently troublesome to prevent the patient from leading a life of normal activity and usefulness. These patients rated at a "market value" might be considered as depreciated; they, however, are unconscious of this depreciation. They are subjectively cured.

The other divisions adopted: greatly improved, failures, made worse, are self-explanatory.

Unfortunately too many medical men as well as surgeons content themselves in giving their *immediate* results and do not bother about noting their *remote* results. It must be said, however, that surgeons have felt such a necessity more keenly than medical men, and in consequence a great number of them have sought to fill the gap.

We sometimes hear of medical men advising against operation because injury to the inferior laryngeal nerve, or to the parathyroids,

may occur, or surgical intervention fails to bring about a cure, or relapses after operation are sometimes seen, or because sometimes myxedema is the sequela of the surgical treatment.

In answer to these objections I will say that with the improvement of our technic, injuries to the inferior laryngeal nerve or parathyroids are rare. When they do occur they are not necessarily serious complications. Furthermore, that surgical treatment is not always successful, no one will deny. But the same result is truer for the medical treatment. There are cases, few in number fortunately, but nevertheless existing, which derive little or no benefit from an operation. As a rule this is due to the fact that the case was beyond repair, or that the operation has been insufficient; the case then belongs to the ones regarded by Kocher as "nicht fertig operiert." However, if the patient is reoperated, then the results become very much more satisfactory, and absolute cure may follow. In some other cases success may fail to respond when the thyroid is not the primary cause, as in the case of Von Haberer's; there thyroidectomy had been of no avail, whereas thymectomy was followed by a marvelous cure.

It is said that there are cases which are made directly worse by the operation; these are rare indeed. I have never observed any in my own experience. To be sure relapses are met with once in a while, but the same is far more true for the medical treatment.

We see sometimes, fortunately rarely, patients who have been operated upon gradually show symptoms of *hypothyroidism*. But the same is true, too, for medical treatment. Have we not said more than once that a thyrotoxic patient left alone, unless he recovers or dies from the disease, is logically destined to become myxedematous? Some internists accuse surgeons of considering as cured patients who are only improved, and of not waiting long enough before publishing their results. The same can be said for internists; they, too, consider as cured cases which are only improved, and they, too, have relapses. How often do we not see Basedow patients who have been treated several times by several different internists and each time have been discharged as cured, come and seek surgical help?

### MEDICAL TREATMENT.

**Rest Cure.**—Rest cure is certainly the best among all the medical means we have at hand to combat Graves's disease. It is the one which was already used by our forerunners in medicine; in fact, it is as old as the world itself. Nature applies it constantly; nature "rests" during the winter from her spring and summer activities. When a muscle has been driven too long, it automatically "rests" in order to recuperate. Sleep is only a forced "rest." In medicine, "rest" is a panacea: the best

medicine for an overburdened stomach is rest; rest is an essential factor for the recuperation of an overdriven heart; it is a necessity for a wrecked nervous system. No wonder then that it was applied to relieve thyrotoxicosis.

There is a great deal of truth in what Crile says, "If the brain could enter into a state of actual hibernation like the bear, it, *i. e.*, thyrotoxicosis, would certainly be cured; but, unhappily, the knowledge of the gravity of the disease itself becomes one of the psychic excitants which aggravate the disease, the entanglement frequently becomes hopeless, and like the Gordian knot, must be cut." I am, however, not convinced that "brain hibernation" alone would suffice to bring about a cure. We often see patients whose nervous disturbances are only second to their other symptoms; these patients are usually moderately nervous, they sleep well, yet, sleep, which is in itself a hibernation, makes little or no difference in their condition. During sleep their organism is still being driven at top speed, the fire does not subside even partially. All this is so because the brain only "hibernates" and not the other organs, especially the thyroid. If the entire organism could hibernate, only then would we have a cure. From this it follows that rest is only an indirect means of treating thyrotoxicosis; it does not attack the causal factor itself, namely, the thyroid, but influences it most by an indirect route, the nervous system.

In order to be therapeutic, rest must be complete; it must consequently be *mental* as well as *physical*. Here, again, it is difficult to set down hard-and-fast rules. The majority of patients will do better far away from their ordinary surroundings. For some the best place is in a sanitarium or hospital; others will find in a sojourn in the country or woods more complete freedom from mental, emotional and physical exertion. These patients should stay and sleep out of doors day and night as much as possible. A sojourn in a moderate altitude, 1000 to 2500 feet, is far more beneficial to them than the seashore, where the majority of such patients are made distinctly worse. Careful inquiry will often elicit some particular etiological factor such as overwork, worry, disappointment, etc., which has been instrumental in fomenting the disease. This, of course, so far as possible, must be eliminated. Talkative friends must be rigidly excluded. The same is true for members of the family from whose petty disputes and vexatious interferences, as Beebe expresses himself, the patient at times stands sorely in need of protection. Only one or two sympathetic and congenial visitors may be allowed to visit for a short time occasionally, and indeed just as a distraction; solitude must not be allowed to become too heavy to bear. It must never be forgotten that thyrotoxic patients are highly sensitive and often react with a veritable thyrotoxic explosion to some



trivial annoyance. The moral comfort, the persuasive, although firm attitude of the physician, and the implicit confidence of the patient in him, are necessary conditions for success.

Thus it will readily be seen that the true "rest cure" is difficult to obtain. Only people of means can follow a real "rest cure," and although with them expense is a secondary matter, even they as time goes by, after months and possibly years have elapsed and the much-longed-for cure is still far away, become discouraged, worried and impatient; the "rest cure" becomes a burden to them. Under such circumstances benefit can no longer be expected from rest.

If this is true for the rich class, how much truer is it for the working class? The necessities of life are imperative with them. They must make their living; they may even have large families to take care of, or they may have a sick husband, father, or mother, to support while they have little or nothing to live upon except what they make. How would you expect them to "rest?" Indeed, they will obey your orders and try to rest, but when after three, five, eight weeks of rest, they see no improvement, when they possibly see that the condition is getting worse, when their financial means are becoming exhausted, or when finally they realize that this "rest cure" may last months or years, and that very likely at the end of that time they will have to be operated upon anyway, they give up in despair, and indeed no one can blame them for it. "Rest cure" for them is impossible; it is illusory. Under such conditions, rest cure is only good as being preparatory to surgical treatment, and not at all as a curative means.

**Medication.**—So long as there is no specific medicine for Graves's disease the little which can be used is based purely upon symptomatic indications.

Digitalis and strophanthus have been used extensively. When organic cardiac disturbances are present this medication has shown itself very beneficial. When the disturbances are purely functional little or no benefit has been obtained. Not infrequently it has proved harmful.

Nervousness and insomnia are treated with bromides, aconite, trional, sulfonal, chloral, veronal and baldrian.

Belladonna and atropine are often beneficial in excessive sweating.

Antipyrine, salicylate of soda and aspirine have been used where there is some fever, neuralgic pain, and especially acute articular rheumatism.

Arsenic is oftentimes not well tolerated, yet it is a valuable remedy. It can be given under the form of Fowler's solution, of pills (*pilulæ asiaticæ*), or of cacodylate of soda subcutaneously. Iron finds little indication.

Glycerophosphate of soda has sometimes given excellent results.

Phosphate of soda has been recommended by Kocher. It must be given in large doses, 6 to 8 grams a day, since only a small proportion of it is absorbed.

Salts of quinine, according to Marquette, act upon the sympathetic and, according to Huchard and Lancereaux, have a vasoconstrictive effect upon the thyroid. What in the Middle West of our country is known as the "Forcheimer treatment" is based upon the use of hydrobromate of quinine and ergotin.

R—Quinine hydrobromate . . . . .	5 grains.
Ergotine . . . . .	1 grain.
D. S.—Three or four times a day.	

Forcheimer was led to use the quinine by noting the favorable action on an individual patient and the fact that "Jesuits' bark" had been advocated in the treatment of goiter. Ergotine was used on the theory that it influenced the size of the bloodvessels. The use of either of these medicines in exophthalmic goiter is empirical, and neither one is particularly indicated. It is nevertheless a fact that some patients have improved decidedly and rapidly with that form of treatment. In many others, however, the effect is scant and not lasting, or totally negative.

The use of iodine and thyroid extracts, is contraindicated.

Intestinal antiseptics may be beneficial in certain cases, especially in those cases where the toxic thyroiditis appears to be of gastro-intestinal origin. High colonic lavages are of good use.

For itching the following formula is sometimes of value:

R—Carbolic acid . . . . .	10.0
Acetic acid . . . . .	200.0
Aq. dest. . . . .	790.0
M. D. S.—For external use.	

Diet.—A simple, good, wholesome, varied diet with plenty of everything is much the best. Wines, tea, coffee, red meats and highly seasoned food should be avoided. Chicken and fish may be allowed. Some patients do well with a diet rich in carbohydrates and fats. Vegetables, especially the leguminous plants, are very beneficial, not only on account of their alimentary quotient and influence upon the motility of the intestines, but also on account of their mineralizing properties. This latter feature is of importance since we know that Basedow patients often eliminate great amounts of mineral salts, especially phosphates and calcium salts. Water must be taken plentifully. Meals should be taken regularly, three times a day, with nothing between times. With some patients, however, it may be deemed necessary to push the feeding by increasing the number of meals. Great care should be taken not to

upset the stomach. Sometimes large quantities of milk, kephir or zoulac, three or four quarts a day, prove exceedingly beneficial. Often, however, this fluid diet is not well tolerated and causes stomach dilatation, hyperacidity, indigestion; in that case the object of the diet is defeated. As a general principle, our aim should be to feed the patient to the utmost with the least tax upon the digestive apparatus.

**Hydrotherapy.**—Hydrotherapy is, too, an excellent adjuvant of the medical treatment. The exact form in which it must be used depends upon the patient. Most patients react well to baths, provided these are of moderate temperature. Such baths, as a rule, have a quieting effect upon the nervous system, enable the patient to sleep better, and tonify the musculature. Some other patients will do better by taking a warm bath first, followed by a cold spray or douche. When vascular symptoms are greatly developed in the thyroid, and when tachycardia is very marked, ice-bags applied on the neck and an ice-cap over the heart are often able to reduce the activity of the thyroid and to mitigate the severity of the cardiac symptoms.

So far as bath resorts are concerned, although a number of them are advertised, especially in Europe, as highly beneficial to Basedow patients, none of them has won fame as a "specific." Whenever I am called upon to give advice in this respect, I always try to send my patients to regions where the water is notoriously goitrogenous in the hope that it will calm down the high, hyperactive epithelium of the thyroid gland. The well-known benefit that Basedow patients derive from a sojourn in mountainous and goitrogenous regions of Switzerland may very well be attributed to this fact.

**Electrotherapy.**—Electric treatment may be general or local. The general treatment portends to quiet the nervous system, and to facilitate the elimination of thyroid toxins. The local treatment tends to influence directly the thyroid, sympathetic, and bulbar centers.

*General Treatment.*—Vigouroux divided Basedow's disease into two large categories: those which have a retarded metabolism, and those which have an accelerated one. According to him electric treatment should not be applied to the second class, as it will only tend to exaggerate the symptoms, especially tachycardia and nervousness; on the contrary, those who have a retarded metabolism will be greatly benefited by electric treatment under the forms of static baths lasting from ten to twenty minutes each time. Baths of high frequency can be given and their efficacy is well supported.

*Local Treatment.*—Vigouroux employs the faradic treatment applied, 1st, on the carotid region; 2d, on the eyes; 3d, on the goiter itself; and 4th, on the cardiac region. The treatment produces diminution of the nervous excitement and favors sleep.

*Galvanic Treatment.*—In the last few years the galvanic treatment has become classical. A large, well-padded electrode, 80 to 120 sq. cms., is connected with the negative pole while another electrode from 150 to 200 sq. cms. is placed on the superior portion of the spinal column and put in communication with the positive pole. The current must be graduated with a rheostat and brusque variations avoided. Thirty to 60 milliampères are used. The treatment lasts from ten to thirty-five minutes every day.

For M. Chartier, the *galvanofaradization* of the thyroid, especially at its vascular poles, of the heart, and of the vagosympathetic system, is the method of choice. A. R. Raineau gives the preference to the continuous electric current. This form of treatment requires a great deal of experience and its intensity must be in direct proportion to the tolerance of the patient, consequently the ampèrage will vary with each given case. The dimensions and nature of the electrode, as well as the polarity to be employed, are important. The method of choice is to place the cathode upon the thyroid; this electrode must be of appropriate size and nature. When such is the case the intensity of the current may run up to 70 milliampères. The current must be started progressively and stopped the same way, otherwise pain will follow. The electrode used for the electric treatment of the eyes is of cup-shape form and must be closely adapted to the eyes. It is filled with moistened cotton and the milliampèrage must be very low.

*Electrolysis* could be employed as a means of reducing the size of the gland, but is painful, requires a great number of applications, leaves a scar, and finally may cause respiratory disturbances on account of connective-tissue degeneration of the gland.

In conclusion it may be said that electric treatment, whatever its form may be, for Graves's disease has often a beneficial effect, especially when combined with other medical measures. Its results, however, are not lasting and are rarely curative. The condition generally relapses as soon as the treatment is stopped.

**Radiotherapy.**—X-ray is known to have a selective, destructive action on highly specialized epithelial cells, especially those of embryological type. It has, consequently, an effect upon the thyroid gland; it reduces its vascularity, its parenchymatous hyperplasia, and thus brings about a sedative and soothing effect due to better regulation of the nervous system. It ameliorates the cardiac condition and diminishes the goiter, but its effects are inconsistent and not lasting. Mayo says: "With x-ray treatment a remission may occur just as remissions occur without treatment, or with other methods of treatment. My experience has been failure or but temporary benefit."



## TREATMENT WITH X-RAYS.

Name and year.	No. of cases.	Cures.	Improvements.	Failures.	Relapses.	Deaths.	Remarks.
1906 Sklodowski, J., Deutsch med. Wchnschr., 1906, xxxii, 1340.	1	..	1	..	..	..	Treated by x-rays. Symptoms relieved but patient not cured in six months.
1911-12 Rinniger, E. M., Northwest M., 1911-12, iii, 44.	4	..	1	1	2		
1913 Boumann, H. A. H., Jour. Lancet, Minn., 1913, xx xiii, 425.	2	..	1	1			
1906 Pfeiffer, C., Beitr. z. klin. Chir., 1906, xlviii, 367.	51	..	2	27	..	22	Treated by x-rays.
1907 Beck, C., New York Med. Monatsschr., 1907, xix, 281.	8	..	7	1	..	..	Treated by x-rays.
1909 Taylor, W. J., Am. Surg., 1909, xlix, 578.	1	1	..	..	..	1	Treated by x-rays. Was made worse.
1910-11 Freund, L., Arch. Roentg. Ray, 1910-11, xv, 13.	23	..	..	20	..	3	Treated by x-rays.
1911-12 Scott, J. N., Jour. Mo. State Med. Assn., 1911-12, viii, 151.	11	..	1	10	..	..	Treated by x-rays. One was subsequently operated upon.
1912 Storey	41	14	22	4	1		Private patients. Hospital cases.
Hooten	14	10	4	..	..	..	
Hooten	17	7	4	4	2	..	
1913 Blitstein, M., Prakt. Aerzt., 1913, liii.	3	..	..	2	..	1	Treated by x-rays.
1913 Turner, D., Lancet, London, 1913, ii, 924.	4	..	..	4	..	..	Treated by radium preceded by x-rays.
1914 Birdsall, E., New York Med. Jour., xcix, 1032.	3	3	..	..	..	..	Treated by x-rays. Only relieved symptomatically
Leonard, C. L., Ibid., 579.	4	..	1	3	..	..	Treated by x-rays.
Sielmann	21	1	1				
1915 Walter	16	8	7	1	..	..	Thymus alone was treated. Patients received 3 series of treatments.
Walter	9	2	5	1	..	..	Thymus alone treated. Patients received 2 series of treatments.
Walter	24	..	some	..	..	..	One series of treatments applied.
1916 Fisher, Ugeskrift for Laeger.	94	..	15	79	..	..	Exophthalmos remained refractory.
Florence Stoney	48	14	22	4	..	..	Seven stopped treatment too soon. One died after operation.
Case, Iowa State Med. Jour.	30	..	..	..	..	..	Claims results as good as can be obtained by surgery.
Rugles, Calif. Jour. of Med.	24	..	..	..	..	..	Improved as regards nervousness, sweating, weight and sleeplessness.
Seymour, Boston Med. and Surg. Jour.	80	..	7.8	..	..	..	Balance improved.

THE SERUM TREATMENT IN EXOPHTHALMIC GOITER.<sup>1</sup>

Date.	Cases reported by.	Method of treatment; kind of serum used.	Previous duration of disease.	Sex; age.	Time under treatment.	Change in goiter.	No. of cases.	Change in exophthalmos and other symptoms.	End-results of cases.
1895	Enriquez	Thyroidectomized dog's blood	....	..	....	..	9	Relieved	In 1903 the writers say that the end-results are disappointing.
1899	Lanz	Thyroidectomized goat's milk	....	..	2 weeks	Less	1	....	General condition very much improved.
1899	Lanz	Thyroidectomized goat's milk, 2 cups daily	....	..	9 weeks	Less	1	....	Very much benefited.
1903	Lanz	Thyroidectomized goat's milk	....	F.	3 months	Same	1	....	Feels completely cured.
1903	Lanz	Thyroidectomized goat's milk, 1 liter daily	3 months	F.	3 months	Less	1	Less	Was bed-ridden before; now is able to be up and at work.
1903	Lanz	Thyroidectomized goat's milk, 1 liter daily	....	F.	3 months	Less	1	....	Much better. Able to go through childbirth without trouble.
1903	Lanz	Thyroidectomized goat's milk	1 year	F. 25	3 months	..	1	....	Great improvement.
1899	Burghart	Myxedema patient's blood, 250 c.c., S. C.	....	.	8 weeks	..	3	....	A great gain in weight and remission of symptoms but can call no case a cure.
1901	Moebius	Moebius's serum	4 years	..	52 days	Less	1	....	{ In both of these cases there was marked alleviation of all symptoms.
1901	Moebius	Moebius's serum	2 years	..	3 months	Less	1	....	
1902	Schultes	Moebius's serum	3 years	F. 45	1½ months	Less	1	....	
1902	Goebel	Thyroidectomized goat's milk	10 years	F. 36	A few weeks	Less	1	Less	General and mental symptoms much improved.
1904	Kuhnemann	Rhodagen 6 grams	6 weeks	F. 19	1 month	Gone	1	Gone	Bed-ridden before, now able to walk a mile without fatigue.
1904	Murray	His own serum	18 months	F. 20	2 months	..	1	Slight change	Moderately good results in both cases but not sure it is due to serum.
1904	Murray	His own serum	5 years	F. 19	3 weeks				
1905	Thieniger	Moebius's serum	....	M.	....	..	1	Better	No change on large doses.
1905	Thieniger	Moebius's serum	....	F.	2 months	..	1	Better	Improved in every way.
1905	Thieniger	Moebius's serum	....	..	....	Less	1	Better	An acute case apparently saved from death by means of the serum.
1905	Thieniger	Moebius's serum	5 days	..	2 weeks	Less	1	Better	

1905 1904	Hempel Moussu	Moebius's serum Parathyroids of a cow	6 weeks ....	F. 55 ..	1 month ....	Less ..	1 1	.... ....	Improved greatly in every way. Gained but died later of tubercu- culosis.
1905 1905 1905 1905	Macculum Roberts Christan Kuh	Parathyroids of a cow Testiculin Thyroidectin Moebius's serum	.... .... .... ....	.. .. .. ..	.... .... .... ....	.. .. .. ..	1 5 18 1	.... .... .... ....	No remarkable results as yet. Marked improvement. All considerably benefited. An excellent palliative but cannot speak as yet as to the permanent results.
1905 1905	Kuh Mix	Thyroidectin Moebius's serum	.... ....	.. ..	.... A considerable period	.. ..	10 1	.... ....	Was bed-ridden, now is able to work.
1905	Mix	Moebius's serum	....	..	A considerable period	..	1	....	Able to work with a complete disappearance of all symp- toms.
1905	Rydel	Rhodagen	....	..	....	..	4	....	A slight improvement but is not sure that it is a result of the serum.
1905 1905 1903	Sigel Ewald Adam	Rhodagen Rhodagen Moebius's serum	.... .... 3 years	.. .. ..	3 months Several weeks 1 month	.. .. ..	2 2 1	.... .... ....	No gain whatsoever. No result. Was unable to work but now has been working for six months. "Cured."
1903	Kirnberger	Rhodagen	....	..	....	..	2	....	In both of these cases there was a disappearance of all acute symptoms and a marked general improvement.
1905 1904 1904 1904 1904	Peters E. von Leyder E. von Leyder E. von Leyder Santton	Moebius's serum Moebius's serum Moebius's serum Moebius's serum Thyroidectomized sheep blood serum	.... 3 years 2 years .... ....	.. .. F. 37 .. F. 35	.... .... .... 1½ years 8 months	.. .. .. .. ..	1 1 1 1 1	.... .... .... .... ....	Good effect. Marked improvement. Feels very much better. Cured in one and a half years. Patient absolutely transformed into a new and healthy woman. Cured.
1904	Santton	Thyroidectomized sheep blood serum	....	M. 31	6 months	..	1	....	A great improvement but had to take the serum right along.
1904	Santton	Thyroidectomized sheep blood serum	3 years	F. 51	21 days	..	1	....	Entirely cured but has to con- tinue the serum.
1914	Rogers	Antithyroid serum	....	..	....	..	..	....	15 to 20 per cent cures; 50 per cent improved; 8 per cent death-rate. A considerable number of failures and relapses.

In advanced cases where other medical means fail to bring about sufficient amelioration to permit some surgical interference, and when the case is steadily growing worse, x-rays may be used to bring about a shrinkage of the thyroid gland and a sufficient diminution of the thyrotoxic symptoms to allow surgery to take place. This treatment has, however, the great disadvantage of creating many adhesions around the gland, thus rendering the operation bloody and difficult. It is, too, a difficult matter to estimate the proper duration of this treatment and the dosage suitable to every case. Furthermore, even in the most competent hands, complications, such as serious burns, may occur.

**Serotherapy.**—Two methods have been in use; the one intending to neutralize the thyroid secretion in the organism itself, and the other, by the use of a thyrotoxic serum, aiming to diminish the secreting surface of the thyroid or to destroy a portion of its secreting elements. The first method is called *antithyroid chymotherapy*, and the second, *thyrotoxic serotherapy*.

\* *Antithyroid Chymotherapy.*—Many attempts have been made in recent years to alleviate the symptoms of Graves's disease by giving the patient milk, serum, or dried blood taken from totally thyroidectomized animals. The principle underlying this therapeutic measure is, that after thyroidectomy, substances, or better antibodies, accumulate in the blood or milk of the thyroidectomized animals. When administered to a thyrotoxic patient, these antibodies neutralize in some way or another the excess secretion of the thyroid. It was suggested by Hunt that the results obtained with the milk of the thyroidectomized animals were due to the milk diet *per se* and not to the formation of antibodies. Edmunds and Trendelenburg concluded from their experiments that in thyrotoxic animals toxic substances accumulated in the blood and milk, and that these substances instead of being antagonistic to the thyroid, had a synergetic action; while Hunt believed that the blood of thyrotoxic animals contained substances which aroused the thyroid gland to increased activity, as is shown by the acetonitrile test. This suggestion is in harmony with the conclusion of Edmunds, who found that the administration of milk of totally thyroidectomized goats to rats fed with thyroid hastened the death of the rats.

The various chymotherapeutic agents are: in France, *hematoethyroidin* of *Hallion*, which is the total blood of thyroidectomized horses; in Germany, the *Moebius antithyroidin* of Merck, which is the serum of thyroidectomized sheep, and which can be obtained either in dried or liquid form, and the *rhodagen* of Burgardt and Blumenthal, which is the dried milk of thyroidectomized goats; in England and America, the *thyroidectine* of Parke, Davis & Co.

All these various chymotherapeutic products are used *per os* and



not subcutaneously or intravenously on account of the symptoms of intoxication, and especially on account of anaphylaxis, which they are liable to cause.

The results from such methods are variable, most of them having resulted in failures. The amelioration obtained is usually only temporary and relapses as soon as the treatment is ceased; furthermore, the treatment is of long duration. Cases of hypothyroidism in connection with their use have been observed by Dunz, Dürig, Murray, Blumenthal and Pitt. It is not said, however, that this hypothyroidism was caused by chymotherapeutic agents themselves, but may have been the natural result of the prolonged overactivity of the gland resulting finally in hypoactivity.

*Thyrotoxic Serotherapy.*—As said before, this method aims to diminish the secreting surface of the thyroid by inhibiting or destroying a portion of its secreting cells. The theory is based upon the researches of Bordet and Metchnikoff, who have found that if repeated injections of crushed products of an organ such as the liver, the kidney, etc., are injected into an animal, there appear in the serum of this animal substances which exert an elective, destructive influence upon the organ similar to the one from which they originate. The serum has become cytotoxic for that organ; since we have a hepatotoxic, a nephrotoxic, and a surrenotoxic serum, we have, too, a thyrotoxic serum.

The first researches were made simultaneously in the same year by various physiologists such as Sartinara, Gontscharukow, Mankowsy. The first attempt with cytotoxic serotherapy in man was made by Murray. Rogers and Beebe, however, have done the most extensive work in that line. In Beebe's opinion the dose used for therapeutic purposes is not actively cytotoxic, the purpose of the treatment being to relieve the toxins and not to cause an immediate destruction of the gland; consequently he regards it as antitoxic.

The thyrotoxic serum is very apt to cause anaphylaxis, either local or general. As Beebe says, the patient complains of intense pain in the back, and experiences a sense of suffocation. The skin becomes flushed and itches intensely; the patient is nauseated, may vomit; and syncope may follow. However, the whole disturbance subsides quickly and the patient, aside from being frightened, is soon all right again. These symptoms are especially apt to occur when erroneously the injection has been made intravenous. Phenomena of local anaphylaxis are characterized by swelling of the arms, pain, redness and erysipelatous-like eruptions.

The results obtained with such therapeutic methods are exceedingly variable and, as seen, are not devoid of danger. According to Lenormant, sudden deaths have followed this form of treatment.

Furthermore, the treatment is painful, long and expensive, and the serum is not always easily obtainable. In the estimation of its most active promoters, this "specific serum" is not "specifically curative," inasmuch as it must be backed up by medical or surgical treatment. It is an adjuvant of either medical or surgical means. The theory upon which it is based is of extraordinary interest, and may some day give us the solution of our problem.

**Polyglandular Medication.**—Ovarian and testicular opotherapy have been used with some success in certain cases and with failures in others. Those cases which were successful were the ones in which Basedow's disease was seemingly dependent upon disturbances of the ovarian function either at the time of puberty, menopause, or pregnancy. On the other hand, in many such cases the results remained negative. Koslowsky, in 1919, claimed to have observed good results in thyrotoxic diarrhea by the use of ovarian extract.

**Thymus Opotherapy.**—The thymus was used for the first time, and accidentally at that, in 1895 by Owen, who had prescribed for his patient fresh thyroid. The doctor saw afterward only that the butcher had mistaken the thymus for the thyroid, yet the result of its use was brilliant. Since then thymic opotherapy has been used with marked success in some cases and again with total failure in others. The thymuses of calves and sheep are to be selected when this method is resorted to.

**Hypophysis Opotherapy.**—Hypophysis opotherapy has been used to alleviate the symptoms of hyperthyroidism with the most varying results. When effective it alleviates the tremor, digestive troubles, sweating and hot flashes; tachycardia diminishes and the general condition of the patient improves. The results, however, are inconstant.

**Parathyroid Opotherapy.**—Parathyroid opotherapy was used with some success by Monson; the case was markedly improved, but relapsed as soon as the treatment was stopped.

**Adrenalin** has been used without great success.

**Pancreas Opotherapy** has sometimes proved beneficial in the fulminating forms of hyperthyroidism of the gastro-intestinal type. Often, however, it has proved a failure. I have employed this medication with the most varying results.

**Polyglandular Opotherapy** is still in its infancy; more trials of it should be made.

**Crotti's Treatment for Exophthalmic Goiter.**—For the past few years I have been using the following formulæ with very good success. In a number of cases the results were remarkable; in others, however, they were negative. I called the first set of tablets *Thyrotoxic Goiter Tablets*, the second, *Polyglandular Tablets*:

THYROTOXIC GOITER TABLETS.

Sodium arsenate . . . . .	0.001
Sodium phosphate . . . . .	0.12
Salol . . . . .	0.1
Sodium bromide . . . . .	0.05
Sodium bicarbonate . . . . .	0.05
Calcium oxalate . . . . .	0.05
(Chocolate coated.)	

POLYGLANDULAR TABLETS

Pituitary gland (desiccated) . . . . .	0.05
Pancreas (desiccated) . . . . .	0.05
Corpora lutea (desiccated) . . . . .	0.05
(Chocolate coated.)	

The thyrotoxic goiter tablets and the polyglandular tablets are prescribed simultaneously. The patient is told to take one of each at the same time, three to six times a day.

Like the simple goiter tablets these tablets have been put up for me by Parke, Davis & Co. I have no objection to having any other firm put them up. These tablets are not patent medicine.

## CHAPTER XXXIX.

### INDICATIONS AND CONTRAINDICATIONS FOR SURGICAL TREATMENT OF EXOPHTHALMIC GOITER.

As we have seen, neither medical nor medicinal treatment, nor radiotherapy, nor serotherapy, is able to compete with surgery so far as results are concerned. Their results are inconstant, incomplete, and insufficient. *Surgical treatment is the method of choice.*

Too, often, however, medical men consider surgical operation in Graves's disease as a means of last resort. They wait too long. They experiment with too many medicaments. In the meantime the disease progresses beyond their control; the organs become vitally damaged, and the outcome becomes more than dubious. Only then, they call in the surgeon to see what can be done: and like Pilate, they too, wash their hands of it all. It must be emphatically proclaimed that this way of doing is unfair: unfair to the patient, because he loses his best chances of a complete cure; unfair to the surgeon, because his efforts cannot be crowned with the success they should; and unfair to future patients. How often do we not see patients in the early development of their disease frightened away from an operation because a hopelessly lost case has been given the "last chance," the one of operation, and has died? On that account an early case, which otherwise would have accepted an operation and would have been cured by it, will hesitate, procrastinate, and thereby lose precious time. Only when the case is too far advanced for assured success will an operation be sought.

Since it is a recognized fact that surgical treatment can be beneficial or curative, and indeed this has been abundantly demonstrated, why wait so long before calling in a surgeon? On the other hand, if one admits that Basedow patients are not surgical, why refer them to the surgeon at all? Why not bear the full responsibility of the decision? So long as thyrotoxic cases shall be referred to the surgeon in the late stage only we shall have the sorrow of registering only incomplete, unsatisfactory results, while the death-rate will continue to be high and failures numerous. It is not the first time that we have had to experience the disheartening lack of support from medical men in some of our big medical problems, as, for example, in the field of appendicitis, gastric, and duodenal ulcer, etc. In such fields we have finally won out. No one today would think of treating medically a case of appendicitis unless



for some special reason. Appendicitis has become a surgical disease, yet, there is no doubt that appendicitis can be cured medically in a number of cases. Why not then remain consistently true to this latter form of treatment? It is because when a case of appendicitis begins, no one knows precisely the course it is going to take; how and when it is going to terminate; whether it is going to perforate, to cause a diffuse peritonitis, or a fistula with one of the intra-abdominal organs, or a thrombophlebitis, an endocarditis, nephritis, hepatitis, or a subphrenic abscess, or a purulent pleurisy, etc., and finally, to cause death. While, on the other hand, if the offending appendix is removed in the early stage of the inflammatory process, all these complications are mostly avoided, and as a result the death-rate is reduced to the minimum. The same is true for thyrotoxicosis. No one can tell what an incipient case of hyperthyroidism is going to do, whether or not it is going to transform itself into a fulminating or a more chronic form of thyrotoxicosis; what the extent of the permanent damage to the organs of the individual will be; how many years the period of invalidity is going to take, and to what extent the depreciation of the individual will amount at last, while, on the other hand, if we operate in the *true incipient stage*, we know from experience that we shall have not far from 100 per cent of permanent cures and practically no deaths. Why should we hesitate then? In my earliest experience I had a number of times the sorrow of seeing patients, to whom I had advised a course of medical treatment for their incipient hyperthyroidism, come back later in a pitiful state. We should never forget that Basedow patients are fragile, that a slight infection, or a benign operation is liable to cause serious accidents; that the more the disease progresses, the more chronic changes take place in the organs, and consequently, the less probable are the chances for success. In order to demonstrate this very thing, Schultze went over the cases operated by Riedl. He divided the cases into three series, the light, the medium, and the severe forms. The light forms gave 100 per cent of cures; the medium forms 6 per cent death and two-thirds of cures, the severe forms 57 per cent success and 28 per cent death.

Kocher, Riedl, Landström, Mayo, etc., all consider surgical treatment as the safest, surest, best and most satisfactory way of handling the disease. A study of the statistics bears out their statements. It is only justice, however, to say that some of the best medical men are fast coming to recognize the necessity of surgical treatment. The example comes from such notable medical clinics as those of Von Noorden, Fr. Müller, and of others, where the cases of Graves's disease which do not respond promptly to medical treatment are advised to undergo surgical treatment. Barker, one of our eminent American internists, said that the treatment of Graves's disease belongs to the surgeon. Lœmke said

the same thing. Osler and Forcheimer advocate surgical treatment in thyrotoxicosis as both logical and scientific.

It would be a mistake, however, to think that every thyrotoxic case should be operated. Each patient is a problem in himself, and only experience and judgment will tell what is the proper thing to be done in each given case. One thing is certain: there is a class of thyrotoxic patients, which, properly handled, can be cured by medical means. To operate on such would be to perform unnecessary operations. On the other hand, there is another class of patients which are, by right, absolutely surgical.

It is often said that any thyrotoxic case which has been under medical treatment for a certain period of time and that does not show any decided improvement, should be turned over to the surgeon. This is, of course, true, but it may sometimes be difficult to decide when medical treatment has become insufficient and when the psychological time to resort to surgical treatment has come. Some authors set down hard-and-rigid rules and claim that if a patient after "six weeks or three months" of medical treatment is not on the road to recovery, he should be operated. Although this is, on the whole, a wise rule, mathematical rules, however, do not fit this disease of such protean and deceiving character. It is not so much a matter of time as it is a matter of judgment. Indications change from one patient to another. There are cases which should be operated at once, and then again there are other cases which could be treated medically for a much longer period of time without running the risk of impairing the chances of success, should an operation eventually have to be resorted to. As Moebius said, "We should not operate too soon, nor too late."

As a matter of fact, we are practically never called upon to operate in cases in which the diagnosis is doubtful. The great majority of cases have been diagnosed over and over again, and repeatedly apparently cured, so that actually from a surgical standpoint the result does not depend so much upon the diagnosis of Graves's disease as it does upon the operable condition of the patient.

When once an operation has been decided upon, the judgment and experience of the surgeon will be largely the determining factors for the safe outcome of the case. Surgeons, because they have done too much, have killed a great number of patients with exophthalmic goiter; also, they have killed many others because they have used a general anesthetic when they should have used a local one, or because they have subjected their patients to an operation near, or at the top of a wave of hyperthyroidism, or because, as someone has said, "They have done the right thing at the wrong time, or the wrong thing at the right time." There is no other field in surgery in which more than in the thyrotoxic field,

the surgeon must be first and above all a good diagnostician. Here he must be able to appreciate the strength of a given heart, to judge how much shock a nervous system will be able to stand and how much it will not; to know whether the case is complicated with thymus enlargement or not, or whether the degenerative processes in the organs have gone so far as to compromise the safety of the operation. Then there comes next the complete mastery of the surgical technic, as the other asset for success. But even then, with the best medico-surgical judgment and experience, every surgeon will sometimes meet with misfortune because the conditions found are deceiving. A heart seems to respond beautifully to a preliminary treatment, but great is our surprise to find that when this heart is expected to stand by us, it simply quits. Again, in another case the wave of hyperthyroidism seems to be tided over; and surgical interference seems to be safe, yet, an acute spell of hyperthyroidism follows the surgical act so that death may ensue. Or in still another case the operation takes place just when an acute spell of hyperthyroidism is in its latent stage. Here the operation acts as an explosive and determines a very acute spell of hyperthyroidism. Then, too, there are unavoidable casualties due to pneumonia, acidosis, nephritis, etc.

It is often said that we surgeons "select" our cases. If by this is meant that we refuse our help whenever there is a risk, simply for the sake of being able to publish beautiful statistics, then it is not true. We all operate thyrotoxic cases whenever there is a chance of bringing about a cure or even relief. But, if it is meant that we do not operate indiscriminately all the exophthalmic goiter patients without giving their condition careful attention and without weighing the chances for success, then the assertion is very true and to our credit. I will say more, it is our duty to do so. It is only by weighing carefully all the minute pros and cons, and by taking into consideration what Mayo calls the "factors of safety," that men like Kocher, Mayo, and many others have reduced their mortality to practically nothing and have obtained such brilliant results.

When men like Crile, for instance, give credit for their improved results and diminished death-rate to their methods, such as anoci-association and nitrous oxide, etc., I feel that they are too generous toward their methods and too unjust toward themselves. They should not forget that in the course of years their medico-surgical judgment has improved, and that experience has taught them that in Graves's disease there is a danger zone which no one dares to pass without great risks; that the surgical traumatism, no matter how small, must be graduated to the resistance of the patient, that there are "factors of safety" which cannot be ignored without punishment. That this must



be so is shown by the fact that men who do not make it a practice of applying the same methods such as anoci-association and nitrous oxide, for instance, have just as good results, to say the least. Who can beat, for instance, Kocher's and Mayo's statistics so far as results are concerned? Yet Kocher's patients, unless physically unfit, walked from their bed to the operating room where surgical preparation was made over again; they underwent the operation under local anesthesia, with the full knowledge that the operation was being performed, and after the operation, as a rule, walked back to their beds. We all know that a painless local anesthesia is a difficult matter to obtain, so that consequently the elements, pain and fear are not absolutely eliminated. Yet his death-rate was less than 1 per cent and his cures between 75 and 80 per cent, while the rest were materially improved. Why should it be so if the whole problem should resolve itself into a question of psychic and painful stimuli? As a matter of fact, the whole secret lies in the careful graduation of the surgical traumatism, no matter if ether, nitrous oxide, or local anesthesia is used; it lies, too, in the careful selection of the psychological time for the surgical venture. All the other conditions are good adjuvants, but not essential.

**What Line of Conduct Shall We Follow in Deciding the Course of Treatment for Each Given Case?**—The following is the one which has served the writer as a guide:

1. A *secondary* or *Basedowified* goiter, whether causing mechanical symptoms or not, is by right surgical. Here thyrotoxicosis is secondary to the presence of that goiter, be it colloid or cystic, or malignant, and as soon as the goiter is removed thyrotoxicosis subsides. These cases are the ones in which the results are among the most gratifying. They respond quickly to the surgical treatment, and provided they are not too bad surgical risks, the death-rate is low.

2. The *early mild forms* of hyperthyroidism in young individuals *should be treated medically*. We often see young women in schools and colleges, girls and debutantes react to overwork and undue excitement with a mild form of hyperthyroidism. They complain of nervousness, palpitation, insomnia, loss of appetite, muscular asthenia; the cardiac action runs up to 100 or higher; they have a moderate thyroid hyperplasia. This class of patients should be the triumph of medical treatment. Such patients should be treated with rest in bed for several weeks or months until the condition has subsided. Furthermore, their activities should be stopped and complete relaxation obtained. Here all physical as well as medicinal means which medical treatment possesses can be applied. Even a few carefully applied x-ray treatments might prove of value in stopping thyrotoxicosis in its embryonic stage. If, however, despite a medical treatment intelligently applied, the condi-



tion shows a progressive tendency an *early operation* should be resorted to in order to bring about a cure. The results are certain, almost 100 per cent, and the death-rate practically negative.

3. The *early typical cases* are *surgical cases*. Just as in acute appendicitis, we do not wait for perforation and general peritonitis to take place, so in these cases we should not wait until the condition has become too severe before interfering surgically. If the patient seeks medical aid for the first time and medical treatment has not been applied, it is well to give it a short but fair trial with the view of preparing the patient for an operation. If in the meantime the condition subsides quickly, all well and good. If not, or if when cured, these cases show a tendency to relapse, then operation should be resorted to without much delay. This is, too, a class of patients where surgery can boast of not far from 100 per cent cure and a low mortality.

In this class of cases the social condition of the patient has an important bearing upon the decision to be taken. If the patient belongs to the more fortunate class, and therefore can devote time and money to recuperation, and even go from one resort to another, the medical treatment may be given a longer trial, *provided the disease loses its progressive character*. But unfortunately a great number of these patients do not belong to this favored class. Either they must make their own living, or they have large families to take care of, or they have to live on what they have saved. It is consequently impossible for them to undergo an adequate course of treatment, with the necessary physical and mental rest and perhaps change of environment before and after treatment. In such cases it would be unreasonable to ask such patients to devote months and years to rest cure and medicinal treatment. The best and only treatment for this class of patients is an early operation. But do not think for one moment that wealth will protect rich patients and save them from surgical treatment. If they belong to the rich class they do not necessarily belong to the privileged class, so far as health is concerned. Indeed I am safe in saying that in Graves's disease the wealthy furnish a heavy contingent of such patients.

4. In the *well-advanced typical cases* no time should be lost before an operation, whatever it may be, is performed. Such cases, as a rule, have already run the gamut of medical means; they have had, off and on, periods of welfare alternating with periods of exacerbation; they have very likely been discharged as medically cured more than once, and each relapse has left them just a little more vulnerable than before. Not only have such cases long since passed the medical stage, but they are also no longer safely surgical. The immediate family should be told frankly that a complete recovery is possibly no longer to be hoped for, and that in that stage the death-rate is higher.

5. The *severe advanced cases* of long standing have, so to speak, *passed the surgical stage*; they have become damaged beyond the possibility of repair; they have *become medical again*. Indeed, in such cases the organic changes in the various organs of the body such as the heart, liver, kidneys, etc., have become so marked that hope of a cure is out of the question. Their whole organism is so completely disorganized, and their resistance so impaired, that an operation as light as it may be is not a procedure to go into without considerable prudence. In such cases if there are reasonable chances for safety for surgical treatment a ligation might be made. When once such patients have withstood the surgical shock it is sometimes remarkable to see how much such a light operation will improve their condition. It will often put them into such a favorable condition that later on they will be able to stand further surgical procedures. We all in our experience have seen similar cases which have been, so to speak, grabbed out of the grave and restored to a life of comparative comfort. But unfortunately it is this class, too, which furnishes the highest mortality. If, for safety's sake, any surgical procedure is forbidden,  $\alpha$ -rays or boiling-water injections may afford some relief, although the prospect for this is not very great; these thyroids have been already "burned out" by the thyrotoxic fire (Fig. 69).

6. The *fulminating forms* of Graves's disease present roughly three types: the cardiovascular, the gastro-intestinal, and the asthenic type, the latter resembling largely the profound physical prostration of Addison's disease. Theoretically, these fulminating forms *should be from the start surgical*; practically, however, most of them *can be only medical*. Indeed, in such cases the symptoms of intoxication are so intense and the progress of the disease so rapid, that there is scarcely any time, except in the early beginning, for surgical procedure. To operate when the wave of hyperthyroidism is at its highest, when the gastro-intestinal symptoms are at their worst, when tachycardia is in the neighborhood of 200 and possibly more, would be to expose the patient to a more or less certain death. In this class of cases anything which is known to be of value in medicosurgical therapeutics must be attempted and that quickly. According to Beebe it is in these fulminating forms that serum treatment has shown its most striking results; and according to him the relief obtained in such cases is quite as striking as that obtained in diphtheria through the administration of antitoxin. If, perchance, during the rapid progress of the condition, there should occur a period of subsidence, a ligation may under local anesthesia be attempted. In the meantime, the  $\alpha$ -rays and boiling-water injections may prove a very efficient means to tide the patient over the dangerous period. When that is done, no time should be lost in performing whatever surgical interference is deemed safe and necessary.

7. As a general principle, any thyrotoxic case which shows a tendency to become chronic or to relapse should be operated. When a case has gone through an acute spell of hyperthyroidism and has subsided, the "interval operation" is the safest procedure.

8. The *fruste forms of hyperthyroidism* are nearly all medical. The patients of this group often show the most bizarre combination of hypothyroidism, hyperthyroidism, and of polyglandular symptoms. Consequently careful analysis of the syndrome should be made in order to derive a rational medical treatment. Only when medical means properly and intelligently applied for a sufficiently long period of time have failed to bring about the necessary relief, can one then resort to operation. In this class of cases the results obtained from operation are slow to show up. On the whole they are unsatisfactory to treat.

9. An acute exacerbation is an absolute contra-indication to operation, no matter at what stage the case may be. It is necessary to wait until this spell has subsided.

10. A patient with a weak and dilated heart, as shown by the Katzenstein test, or one with a low blood-pressure, is one in whom the dangers of any surgical treatment are greatly increased. This class of cases should be treated medically until an operation can be deemed safe. If, however, the case grows steadily worse, it then becomes an emergency one in which something must be done. In that case the surgical traumatism must be graduated to the patient's condition.

11. A certain degree of myocarditis, or of valvular lesions, provided they are well compensated, or a moderate amount of glycosuria, is no absolute contra-indication to operation.

12. The presence of a thymic hyperplasia is by no means a contra-indication for operative treatment, but rather a strong indication in its favor. In my practice thymectomy is performed as a routine procedure in every goiter operation whenever thymic hyperplasia is present.

13. Should a patient who has been operated on not improve in the manner in which he is expected to, or, after a period of welfare, should he relapse, this does not indicate a failure of the surgical principle. If a medical case does not improve sufficiently, or relapses after a period of improvement, the treatment is renewed with more energy. The same is true for surgical treatment. A number of these cases belong to that class of patients which Kocher considered as "nicht fertig operiert."

14. As a general principle, in exophthalmic goiter surgery, it is better to err in favor of conservatism, and when in doubt, it is by far safer to ligate instead of to thyroidectomize, and to resort to two ligations instead of three, one instead of two. It is better to have an imperfect result than it is to have death, inasmuch as the first alternative may be remedied by a subsequent operation, whereas the latter is beyond one's reach.

15. When once a patient has been operated on, he becomes again a *medical patient*. He should be followed medically until cure is assured. The same medical principles which apply prior to the operation find their indication and usefulness after the operation: rest, change of environment, automobiling, sojourn in mountainous regions, are the best adjuvants of the surgical treatment.

As seen by this outline, Graves's disease is a *medicosurgical* disease, and one in which both the physician and surgeon must have something to say. The physician prepares the road for the surgeon and when the work is done, gives it its finishing touch. Great things today are not done by the individual alone, but by coöperative work. There is no other field in medicine where the "teamwork" principle can be applied to better advantage. We often hear some internists ridicule the fact that surgeons require their patients to follow a course of medical treatment after their operations. Why, that is the most logical thing to do! Indeed, since the systemic disturbances are often very marked, although the primary cause, namely, the thyroid, has been removed, it will, nevertheless, take quite a long time before the organism finds its normal equilibrium again. The entire complicated machinery of the organism must readjust itself. No one will think of feeling shocked because gastroenterostomy for gastric ulcer, gastric resection for cancer, will require a postoperative medical assistance for quite a long time. Why, then, feel scandalized, for exactly the same thing in thyroid surgery? Let it be said that petty disputes will not advance the matter any, and, be it as it may, if it is to the better advantage of the patients to so treat them, let us do so.

Medical men, says Halsted, have every right, if they so choose, to try non-surgical measures in the early stages of the disease. But if, failing not only to arrest the disease but also to cure their patients quickly, they do not advise operation in the safe and curable stage, they should be held to as strict accountability as when they fail to call for surgical help until a patient with acute appendicitis, for example, has developed a general diffuse peritonitis. Let us recall the words of our great master, Kocher, when he said, speaking to the internists, "Gentlemen, do not fail to send us your patients early. We will send them back to you, and in so doing will find in our work better results and more pleasure."



## CHAPTER XL.

### SURGICAL TECHNIC OF OPERATIONS UPON THE THYROID GLAND.

SURGICAL technic in goiter operations has improved enormously in the last fifteen years. These results are especially due to Kocher and his school, to the German school, of whose members, Wölfler, Billroth, Mikulicz, von Eiselsberg, and a few others rank first; to the French school, especially that of Lyon counting Poncet, Berard, Delore and Alamartine among its first members. In America, Charles H. Mayo, Ochsner Halsted, etc., have done their share toward generalizing and improving thyroid surgery.

A uniform technic does not exist. Every surgeon puts into his work the seal of his own individuality, consequently divergence of details will always be found; fundamental differences, however, do not exist any longer.

Good surgery must always be based upon the exact knowledge of the anatomy, physiology and pathology of the organ against which it is directed. It must take into consideration, too, certain desiderata and certain principles which must be aimed at if one wishes to obtain the maximum of results from the operation. Fifteen to twenty years ago the main thing was to have the goiter out, no matter how or at what cost. To be sure, the scar was not always very pretty, while the inferior laryngeal nerve did not always escape injury, and a slight touch of tetany was not to be wondered at. Then, too, some hypothyroidism was only too natural and lucky it was if it did not develop into a full myxedema! Today these views are no longer acceptable. Our knowledge of the condition has advanced; our technic has become more precise, and then, too, the public has become more critical. Consequently before going into the description of the operation itself let us go over the anatomical and pathological conditions in which an operation takes place; let us decide what is anatomically important and what can be left out; let us discuss, too, these different requirements which give to the technic its present characteristics.

Before going any further let us ask:

What are these desiderata?

We want:

1. To have constantly present in our minds a few particular anatomical facts from which will derive certain important technical procedures.

2. To leave the parathyroids and the inferior laryngeal nerve uninjured.

3. To leave enough thyroid tissue so as to protect the patient against future hypothyroidism.

4. To protect the patient against future relapses.

5. To obtain as fine and as nearly invisible a scar as is possible.

6. To shape the neck so as to render it pleasing to the esthetic sense.

**Anatomical Facts.**—Surgery of the thyroid became simple the day when surgeons learned to utilize the normal and pathological intra- as well as perithyroidal planes of cleavage.

Let us suppose that we make a transverse incision in the thyroid region of the neck, and retract the upper and lower cutaneous flaps in their respective directions, we shall then find:

1. The sternocleidomastoid muscles and the prethyroidal muscles, which are the sternohyoid, omohyoid and underneath, the sternothyroid muscles. These muscles are covered by the *superficial cervical fascia*. Starting from the ligamentum nuchæ this fascia forms a sheath for the trapezius muscle, passes over the entire posterior triangle of the neck until it reaches the posterior border of the sternocleidomastoid muscle. There it forms a sheath for this muscle, passes over the anterior triangle of the neck, and finally meets in the middle line the superficial cervical fascia from the other side.

2. Extending from one omohyoid muscle to the other, and from the hyoid bone to the manubrium sterni and to the middle of the clavicles, the *middle cervical fascia* forms a sheath for the three thyroïdal muscles, goes toward the middle line and there fuses with the one of the other side and the superficial cervical fascia, thus forming the *cervical linea alba*.

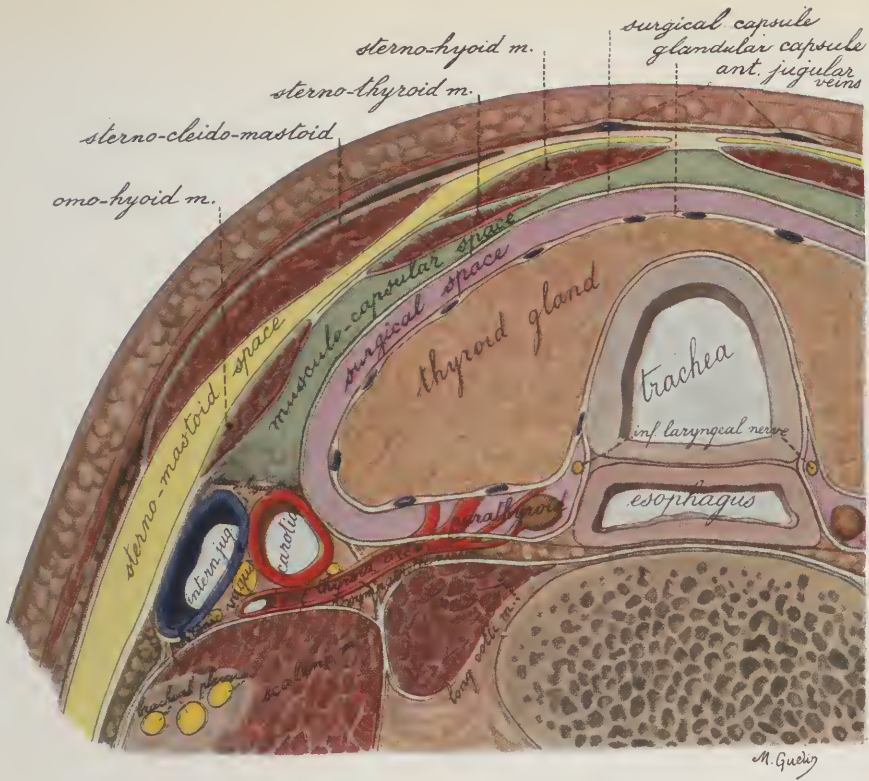
3. The middle cervical fascia and the prevertebral fascia give origin to a loose connective-tissue capsule which surrounds the thyroid gland and is easily detachable. Let us call that capsule the *surgical capsule of the thyroid*. (Plate XI, Fig. 1.)

4. The thyroid parenchyma is surrounded by a capsule which is the equivalent of the one seen in other glandular organs such as the capsule of Glisson for the liver, the albuginea for the testicle, the renal capsule for the kidneys, etc. It is in close relation with the parenchyma and sends inwardly septa dividing the parenchyma into lobi and lobuli and finally surrounds each alveoli with a very thin layer of connective tissue, the *glandular capsule*. (Plate XI, Fig. 1.)

5. Between the sternocleidomastoid muscles and the prethyroid muscles there is a *normal plane of cleavage*. De Quervain calls it the *sternomastoid space*. (Plate XI, Fig. 1.)

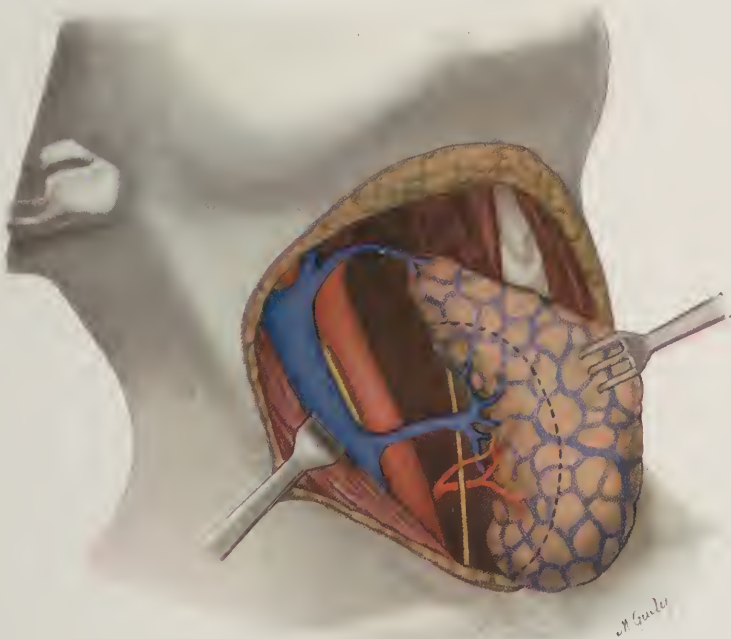
# PLATE XI

FIG. 1



Cross-section of the Neck with its Various Organs, Showing the Relation of the Thyroid to the Neighboring Tissues and the Various Spaces Described in the Text.

FIG. 2



## Danger Zone.

The relation of the carotid sheath, inferior laryngeal nerve, inferior thyroid artery, middle vein, parathyroids, and of the posterior surface of the thyroid gland to each other. The dotted curved line shows where resection should take place in order to avoid injury to these various organs.





6. Between the prethyroid muscles and the surgical capsule there is another plane of cleavage, the *musculocapsular space*. (Plate IX, Fig. 1.)

7. Finally, between the glandular capsule and the surgical capsule there is another plane of cleavage formed of loose connective tissue and containing numerous arteries and veins, the *intercapsular* or *surgical space*. (Plate XI, Fig. 1.) It surrounds the thyroid gland entirely and extends from one side of the trachea and the esophagus to the other side.

The relations between the glandular capsule and the surgical capsule are, as a rule, very loose. It is only on the postero-internal surface of the thyroid that they come into a more intimate contact; between them a great number of arterial and venous branches are found going in and out through the glandular capsule. Inwardly, since the thyroid is inti-

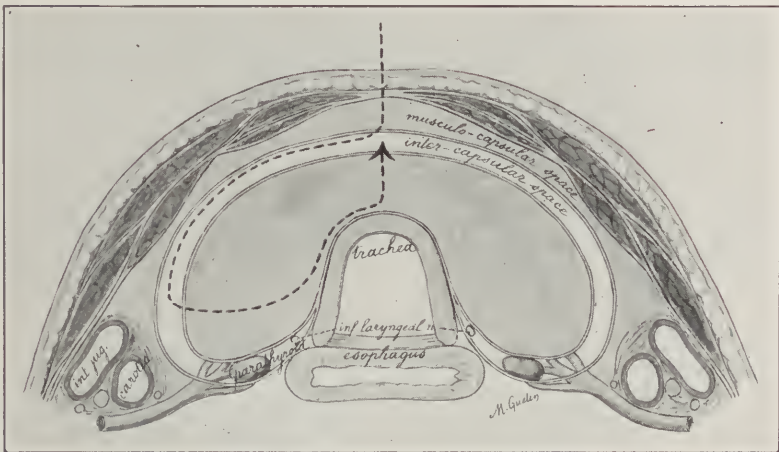


FIG. 79.—Showing proper plane of cleavage which must be entered into before attempting resection of the thyroid. Showing, too, how much thyroid tissue should be left in contact with the danger zone in order to avoid accidents. The intercapsular space is the same as the surgical space.

mately adherent to the trachea, no plane of cleavage may be expected to be found there. In the posterior portion of this perithyroid cellular space we find the parathyroids and the inferior laryngeal nerves. Consequently we must regard the posterior portion of this perithyroid cellular space as the *danger zone* which the surgeon must carefully avoid during operation. (Plate XI, Fig. 2.)

Such are the anatomical facts grossly described. It is obvious that the musculocapsular and the surgical spaces are the most important so far as the surgical technic is concerned. The surgical space is the "good plane of cleavage" (Fig. 79), which must be looked for if the surgeon wishes to make an easy and brilliant thyroidectomy. The surgical capsule must have been opened and the surgical space found before attempting

to dislocate the goiter. On the other hand, its postero-internal region must be absolutely avoided unless one wishes to expose the patient to tetany by injuring the parathyroids, or to vocal disturbances by injuring the inferior laryngeal nerves. For the same reasons, it follows, too, that when resection of the thyroid is being performed, one should purposely avoid retracting the surgical capsule over its entire course: such retraction should take place only just enough to allow manipulations on the thyroid to take place easily. It follows, furthermore, that in order to avoid injury to the parathyroids and inferior laryngeal nerves, the *danger zone* must be left undisturbed. (Plate XI, Fig. 2.) This is best obtained by leaving a layer of glandular tissue in contact with it while resection is being made.

The following fact is interesting: the carotid sheath is entirely independent of the spaces above described, for it possesses a space of its own: the *carotid space*. This was demonstrated by De Quervain by injecting the sheath of the vascular cord at the angle of the jaw with gelatin. The gelatin followed the vascular cord over its entire course, filled it up, but did not fuse in any way with one of the other planes above mentioned. The inferior thyroid artery passes behind the carotid space but does not penetrate into it. This is of great importance for the ligation of the inferior thyroid artery, as the carotid sheath can be strongly retracted without exposing the inferior thyroid artery to injury.

**Pathological Planes of Cleavage.**—So much for the normal planes of cleavage. The pathological ones are very important, too, and should be known. They are found mostly in nodular goiters, cystic or colloid, and must be always taken into consideration when one wishes to perform an enucleation. In nodular goiters the pathological plane of cleavage is intraglandular and lies all around the nodule. It is formed by the thickened enveloping membrane of the nodule itself, and by a connective-tissue formation all around it due to the chronic pressure of the nodule on the parenchyma. Between these two layers of tissue lies the proper plane of cleavage. (Figs. 80 and 83.) As soon as it is found enucleation takes place easily. If the nodule lies at the periphery of the lobe and comes in contact with the glandular capsule, the latter capsule may fuse together with the nodule so as to destroy entirely at that point the plane of cleavage. This plane, however, can be easily found by making an incision in the neighboring parenchyma and going through it until the nodule is reached.

**Blood Supply of the Thyroid.**—It had been thought for a long time that the thyroid arteries were *terminal*. These conclusions were based mostly on the researches of Hyrtl, Anna Begoune, Jaeger-Luroth, etc. Other anatomists, however, as Sappey, Cruveilhier, Thane, etc., objected

# PLATE XII

FIG. 1

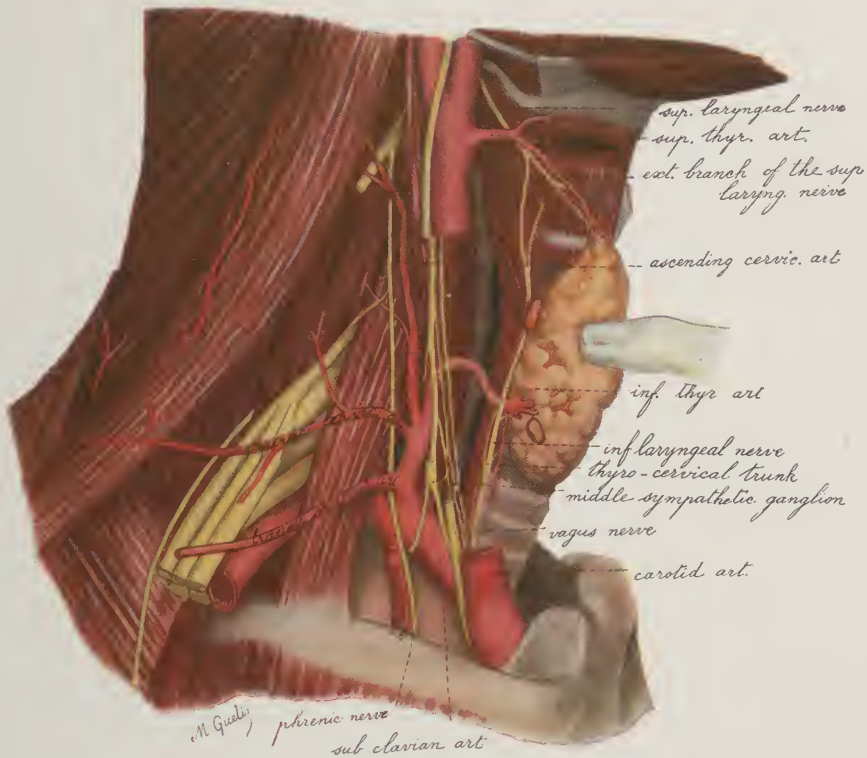


*M. Quelly*

## Intracapsular Resection.

Showing the thin capsule which remains after decortication of the thyroid, also how easy it would be to injure the parathyroids and inferior laryngeal nerve. These organs are seen by transparency through the thin capsular veil. Note, too, the longitudinal anastomosis between the superior and inferior thyroid arteries.

FIG. 2



## Normal Anatomy of the Deep Cervical Organs Showing Their Interrelation.

The relation of the inferior thyroid to the sympathetic and the inferior laryngeal nerve is plainly seen.





to these conclusions. From a practical standpoint it was important to settle this question one way or another: indeed, if the thyroid arteries were terminal, ligation of one of them would expose the territory of the gland supplied by this artery to necrosis. On the other hand, if they anastomose freely, ligation of one of them would not have any material effect upon the intraglandular circulation; this is especially important in exophthalmic goiter work. Lately, Landström, Delore and Alamartine have reviewed this question. The writer has done some research work in that line by injecting through one or more of the thyroid arteries a 20 per cent benzin solution of vermilion and controlling the results with *x*-rays. The following conclusions may be drawn: the superior and inferior thyroid arteries anastomose freely by an intricate mingling of their terminal branches and by several longitudinal anastomoses: the most constant and most important one of them follows its course in the tracheo-esophageal angle. (Plate XII, Fig. 1.) Bilateral transverse anastomoses exist, too, between each lobe. They are less numerous and vary greatly in volume, and they connect mostly the two superior thyroid arterial systems. The most important of them is the cricothyroid branch which lies just above the upper border of the isthmus and connects the anterior branches of the superior thyroid artery. This communicating branch is the one which is severed when performing the cricothyroid tracheotomy. Very often there is another transverse anastomosis a little higher up, crossing transversely in front of the cricothyroid membrane and connecting the two superior thyroid systems. Besides these two important bilateral anastomoses there are many smaller ones connecting the branches of the two superior arteries, of the posterior longitudinal anastomosis and of the cricothyroid arteries: they form a very intricate and most variable arterial plexus.

The two inferior thyroid arteries communicate with each other, as a rule, through anastomoses connecting the longitudinal anastomosis of each side. However numerous these anastomoses are, it would be an error to believe that they would be able to take up, offhand, the blood supply of the territory whose feeding artery has been severed. To a certain extent this is true for the arteries of the same side, for the superior artery supplies very rapidly and abundantly the territory of the inferior thyroid when the latter one has been ligated, and *vice versa*, intraglandular anastomoses being very abundant and very effective. It is no longer quite so true for the interlobar anastomoses: these are less abundant and less effective. There really exists between the two lobes a certain vascular independence, although not complete. De Quervain very judiciously remarks that we already knew clinically what these researches brought to us. Indeed, if after ligation of the superior and inferior thyroid arteries of one side, resection of the lobe is undertaken,

one can see plainly that the arterial hemorrhage is still going on, though much diminished. I think every surgeon can vouch for that.

Besides its own vascularization the thyroid gland possesses another vascular supply coming from the neighboring tissues, especially the trachea and esophagus. Landström, Delore and Alamartine finally found a diffuse system of anastomoses connecting the superior arteries with the prethyroid muscles and subcutaneous tissues. This entire collateral supply is quite important and is sufficient to prevent necrosis of the thyroid after ligation of the four thyroid arteries.

In conclusion we may say that the thyroid arteries are not terminal. One, two, three, even all four thyroid arteries can be ligated without exposing the gland to necrosis: sufficient vascular supply takes place through the collateral anastomosis from the neighboring organs, even if the ima artery should not be present.

Which one of the thyroid arteries is the more important, the superior or the inferior? The opinions are divided. Von Eiselsberg and the majority of German authors consider the inferior thyroid as the main one, the superior being only a secondary artery. De Quervain regards the inferior thyroid artery as the one which is the more important. The same does Halsted. He believes that the inferior thyroid is usually larger than the superior vessel which is subject to greater changes because of the inconstant position of the superior pole. Delore and Alamartine do not share the same view. They believe that the superior thyroid artery is the more important.

In the superior vertebrates it is the one most constantly found, whereas the inferior thyroid is not. The superior thyroid is more constant in its caliber, in its mode of division, and in its course. Its branches of division cap the superior pole. The superior thyroid artery follows the upper pole in all its changes, be it changes in form or position: where the upper pole is, there the superior thyroid will also be found. The upper pole is the best landmark for the position of the superior thyroid, and the upper pole is always easily found. The inferior thyroid, on the other hand, is much more variable in its position and volume. It does not cap the inferior pole as does the superior thyroid for the upper pole, but passing behind the vascular cord, approaches the gland laterally at the junction of the lower with the two upper thirds, goes, more or less, far behind the posterior surface and only then penetrates the thyroid gland. (Plate XII, Fig. 2.) Like the superior thyroid, it follows, too, the thyroid gland in its changes of form and position. If the inferior pole becomes greatly enlarged, the inferior thyroid artery becomes somewhat displaced, but never to such an extent as to become intrathoracic, for instance. Furthermore, the inferior thyroid artery divides into several branches, sometimes very far from its point of

entrance into the thyroid gland, so that it is not uncommon to see a surgeon ligate one of these branches, thinking that he is dealing with the main trunk of the artery. Finally, that the inferior thyroid artery is of much more difficult access for ligation than the superior, and on the whole offers more dangers than the ligation of the superior thyroid artery, and again that its main trunk or its branches of division mingle sometimes in a very intimate way with the parathyroids and especially the inferior laryngeal nerve (Plate XII, Fig. 2), is a reason why a great many surgeons *a priori* prefer to deal with the superior artery rather than with the inferior. Hence possibly a reason for their divergence of opinion.

In the writer's investigations he has found that if normal glands only are taken into consideration, the difference in caliber between the superior and inferior thyroid arteries and the difference in their position are only slight. This I have had the opportunity to observe time and time again when demonstrating normal anatomy. In 2 per cent of the cases the inferior thyroid artery is found absent. In that case a large ima artery is often seen to take its place. At the same time there is a huge superior thyroid; obviously this anatomical fact is an ideal one so far as polar ligation is concerned, inasmuch as after ligation of the upper pole the lobe would be robbed of its greatest source of blood supply. In pathological thyroids I have seen the superior thyroid decidedly larger than the inferior thyroid, and *vice versa*. I have the impression, however, that in simple goiters, especially those of large size, the inferior thyroid artery is decidedly larger than the superior, whereas in thyrotoxic goiters the superior seems to have a larger caliber.

**Parathyroids.**—In animals, especially in dogs and cats, the parathyroids are *internal*, namely, are situated in the parenchyma itself of the gland. In man the parathyroids are *external*; they are nearly always located outside of the glandular capsule. Some aberrant parathyroid tissue, however, may be found in the thyroid parenchyma. Getzowa states that when a superior parathyroid is missing it is nearly always replaced by intraglandular parathyroid tissue. While working in the pathological laboratory at Lausanne, Switzerland, with my master, Professor Stilling, I made the examination of 75 cadavers in order to determine the number and position of the parathyroids. I found: 4 times, 1 parathyroid (twice the upper, and twice the lower); 32 times, 2 parathyroids; 26 times, 3 parathyroids; 11 times, 4 parathyroids; 2 times, no parathyroids at all, but instead, some parathyroid tissue diffusely imbedded in the fat and areolar tissue throughout the entire postero-internal region of the thyroid and easily recognizable by its orange-yellow color. From these findings it follows that the stereotyped conception of two superior and two inferior parathyroids is far from being correct. In the cases where I found only 1 parathyroid this little



glandule had apparently undergone a compensatory hypertrophy, as all four times they were larger than they usually are. One of them was not far from the size of a pea.

With what we physiologically know of the parathyroids it is difficult to accept the opinion that the parathyroids may be totally absent. MacCallum is quite correct when he says, "Because in a space extending from the basis of the skull to the diaphragm we do not find a little gland the size of a lentil, have we the right to deny its existence?" The same author concludes that the number of parathyroids is, as a rule, in direct proportion to the patience and persistence of the searching anatomist.

If, on the one hand, the parathyroids may be diminished in number, they may, on the other hand, be found more numerous than normally; for instance, Harvier, Thompson and Harris found 5 parathyroids; Schaper and Berkeley, 6; Getzowa, 7; Zuckerkandl, 8; and Erdheim, 12.

While the position of these glandules may vary, their variation is within certain definite limits. The superior parathyroids are more constant in position than the inferior ones. The superior parathyroids are found, one on each side, in the vertical groove between the esophagus and the thyroid at the junction of the upper third with the two lower thirds of the thyroid gland (Fig. 79, and Plate XII, Fig. 2); this is about at the level of the cricoid cartilage. As a rule they are wholly outside of the glandular capsule. The arterial branches and the inferior laryngeal nerve pass up in front, and internally to them. The inferior parathyroids lie generally more laterally than the superior ones. They are found at the junction of the lower third with the two upper thirds of the thyroid and are external to the inferior laryngeal nerve and the inferior thyroid. (Fig. 79 and Plate XII, Fig. 2.)

Of course a great many variations are met with, especially for the inferior parathyroids. They may be found at the extremity of the lower pole, under the lower border of the isthmus, in the pre- or peritracheal fatty tissue, or even imbedded in the thymus gland.

After the careful researches of Evans, Halsted, Ginsberg, Welsh, Geiss, etc., we know that the parathyroids get their blood supply from a branch of division of the inferior thyroid artery through a small vessel which is called the *parathyroid artery* and which supplies both the superior and inferior parathyroids. Only rarely the superior thyroid artery gives off a branch destined for the superior parathyroids: in such instances these two small parathyroid arteries, the one destined for the superior parathyroid and the other destined for the inferior parathyroid, may anastomose together. Not so infrequently both superior and inferior parathyroids get their blood supply independently from a small collateral bloodvessel coming off directly from the posterior longitudinal anastomosis which runs on the inner posterior border of the thyroid gland and connects the superior with the inferior thyroid arterial system.



It had been thought for a time that there was no other source of blood supply than the one given by the parathyroid artery; consequently if these little glandules were deprived of their only known blood supply, they would not get any nourishment from another source; their fate would be the same as that of a transplanted gland. This is not quite correct. We know that there exists between the parathyroid and the thyroid capsule a fine collateral circulation. Another collateral circulation especially for the superior parathyroids is secured by fine arteries coming from the pharynx, esophagus, trachea. Furthermore, Ginsberg has shown that the secondary blood supply for the parathyroid glands is secured by anastomotic channels from the opposite side. The importance of this collateral circulation is too obvious. It allows us to ligate the four thyroid arteries without running too great risk of parathyroid insufficiency. These facts are in perfect concordance with our clinical experience. It is true that twice tetany has occurred as a consequence of the ligation of the four thyroid arteries. These two cases were reported by Kocher and von Eiselsberg. They are the only two cases recorded. Why this occurred, no one knows. Possibly there were some vascular anomalies, possibly, too, the parathyroids of the other side were absent and the only one or two glandules present were inadvertently traumatized. Perhaps these patients were already in a state of latent hypoparathyroidism: some slight disturbance in their anatomical or functional equilibrium was sufficient to throw out of gear the entire parathyroid mechanism. Whatever the cause may have been, similar consequences have not been reported since. De Quervain, who has performed quite often the ligation of  $3\frac{1}{2}$  out of 4 thyroid arteries, namely, the two inferiors, one superior and the anterior branch of the other superior, has never noticed any signs of tetany.

**Recurrent Laryngeal Nerves.**—The inferior or recurrent laryngeal nerve is the motor nerve of the larynx. It is a branch of the vagus nerve. It arises on the right side in front of the subclavian artery, winds from before backward around that vessel, and ascends obliquely to the side of the trachea behind the common carotid, and either in front of or behind the inferior thyroid artery. On the left side it arises in front of the arch of the aorta and winds from before, backward around the aorta at the point where the impervious ductus arteriosus is attached and then ascends to the side of the trachea. The nerve on each side ascends in the groove between the esophagus and the trachea, passes either anteriorly or posteriorly, or more often, between the branches of division of the inferior thyroid artery (Plate XI, Fig. 2), enters the larynx, piercing the cricothyroid membrane behind the articulation of the inferior horn of the thyroid cartilage with the cricoid, being distributed to all the muscles of the larynx except the cricothyroid.

These anatomical considerations show that the inferior laryngeal nerve, too, lies in the "danger zone," namely, the postero-internal portion of the thyroid gland.

**Conclusions Drawn from Anatomical Facts.**—1. The postero-internal surface of the thyroid gland must be considered as the *danger zone*; there are found the parathyroids and the inferior laryngeal nerves (Fig. 81).

2. The surgical capsule should be detached and retracted just enough to allow the different steps of the operation to be performed easily, and especially the luxation of the goiter. This capsule should be left *in situ* and in its relations with the thyroid in the entire postero-internal region of the gland, and the luxation of the goiter should not be pushed too far (Plate XXIII), so as not to disturb the collateral circulation between the parathyroid glandules and the neighboring tissues, and further, not to run the risk of injuring the inferior laryngeal nerve.

3. Ligation of the inferior thyroid artery should be done far from its point of entrance into the thyroid gland (Plate XXIII). The "ultra-ligation" of Halsted is a dangerous method. It should be remembered that not so infrequently the parathyroids are situated between the branches of bifurcation of this artery, consequently if ligation takes place near the glandular capsule the parathyroids are exposed to injury. The same is true for the recurrent laryngeal nerve.

4. Total unilateral intracapsular excision of the thyroid should be discarded because of the danger of injuring the parathyroids and inferior laryngeal nerves (Plate XII, Fig. 1). Resection is the method of choice, as it leaves a more or less thick sheath of glandular tissue in connection with the danger zone. A well-managed enucleation does not expose to injury the parathyroids.

5. The collateral circulation with the neighboring tissues is so well developed for the thyroid and for the parathyroids that ligation of the four arteries can be performed without running any risks of tetany, provided that the "danger zone" is left undisturbed.

### EXCISION, RESECTION OR ENUCLEATION?

As in any other surgical field, the surgeon doing thyroid surgery must have at his disposal several technical methods in order to be able to meet all emergencies successfully. He must adapt his technic to the case and not suit his case to his technic. As De Quervain says, "It is no longer enough to know what should be done in a general way, but what should be done in each particular case." In doing thyroid surgery to what method shall we resort? Shall we adopt *excision*, *resection*, or *enucleation*, as the method of choice, or shall we use a combination of these various methods? In going over the medical literature one can but

be impressed by the confusion which exists in the denominations of the different surgical procedures. Nearly always the terms, excision, enucleation, resection, thyroidectomy, lobectomy and extirpation of the thyroid are used indiscriminately.

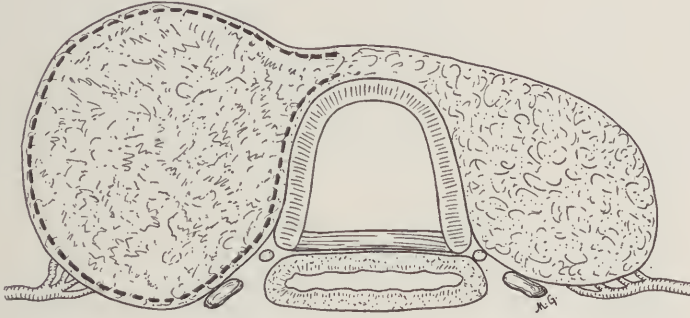
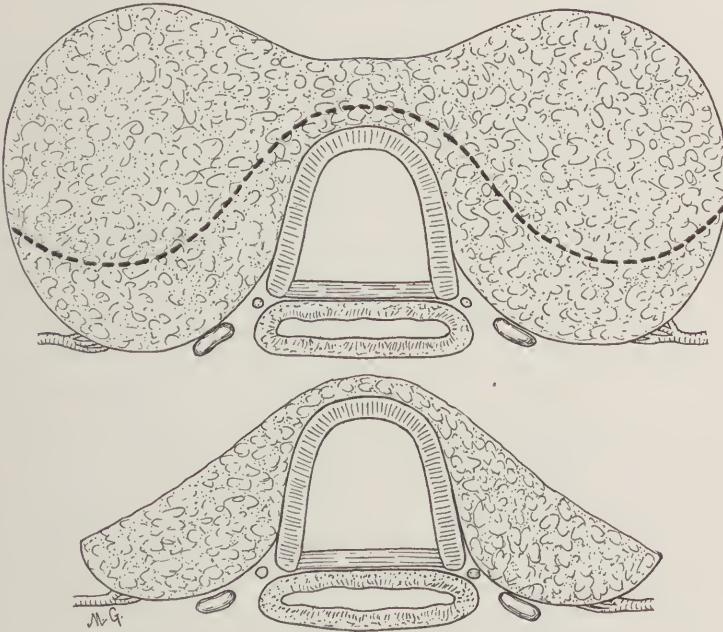


FIG. 80.—Intracapsular excision.

**Excision.**—Excision was used by Kocher to demonstrate the complete removal of one lobe without leaving anything of the posterior portion of the gland (Fig. 80). Excision can be *unilateral* or *bilateral*; total excision can take place only in malignant goiters.

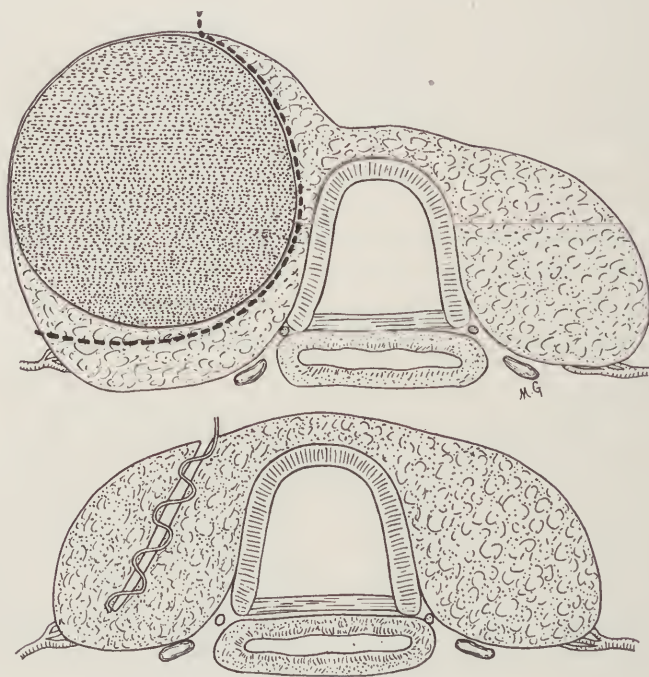


FIGS. 81 and 82.—Transglandular resection.

**Resection** (Mikulicz) means the partial extirpation of the thyroid, a portion of the glandular tissue being left *in situ*. Resection, too, may be *unilateral* or *bilateral* (Figs. 81 and 82).

**Enucleation** means the peeling off, the decortication of one or several intraglandular nodules (Figs. 83 and 84).

The other denominations, as thyroidectomy, lobectomy, hemithyroidectomy, have only a general meaning. They do not convey in any way the idea of how the removal of the goiter is being done, namely, if excision, resection, or enucleation has taken place. Consequently I shall use them when speaking in a general way of the fact that an operation has been performed on the thyroid without trying to indicate precisely the mode in which this operation has been performed.

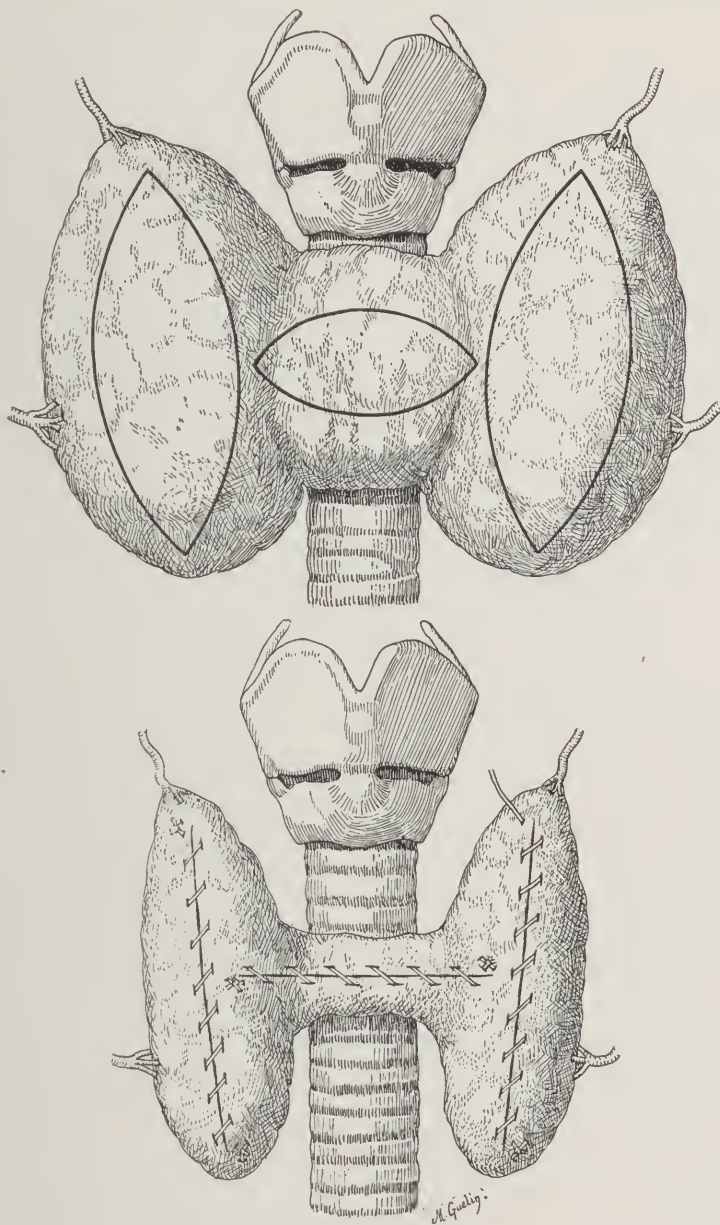


FIGS. 83 and 84.—Enucleoresection.

Inasmuch as excision exposes too easily to injury the inferior laryngeal nerves and parathyroids, this method has been more or less abandoned as such. Kocher advocated and practised it, but left a small portion of glandular tissue in contact with the danger zone, consequently, properly speaking, this surgical procedure is no longer a true excision, but becomes a resection. The intracapsular or subcapsular excision which is performed by some of our American surgeons, and which may be compared to a total decortication of the lobe is, too, for the same reasons to be discarded. (Plate X, Fig. 1.) Not very long ago I saw one of our foremost surgeons, when performing this intracapsular excision, come in contact with a parathyroid, crush it with a hemostat,



and become aware of it only when his attention was called to it by one of his assistants. Iversen reports a case operated by Rovsing in which both



FIGS. 85 and 86.—Cuneiform resection.

parathyroids were accidentally removed with the excised lobe, although intracapsular excision was undertaken with the special view of safeguarding the parathyroids and inferior laryngeal nerves. Halsted in 40

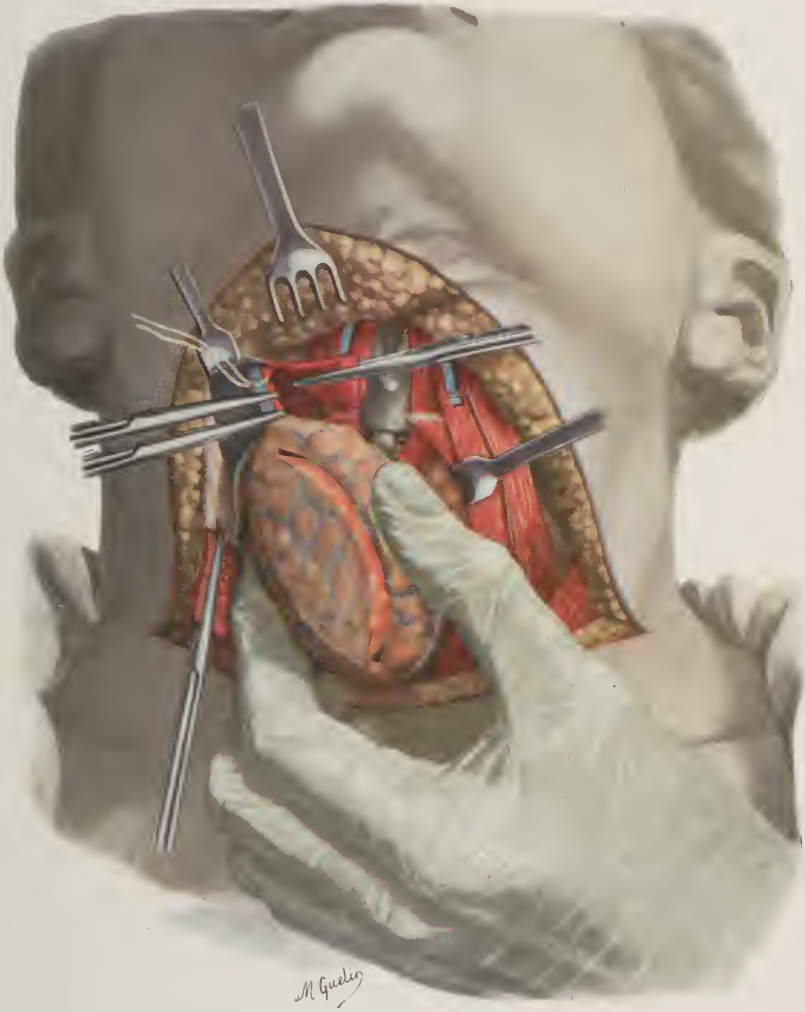
subcapsular excisions removed one or two parathyroids with the excised lobe *only* 7 times! These accidents, of course, would never have occurred if resection had been performed. There may have been an error in technic; they should have remained intracapsularly. Theoretically this may be true; practically, however, it is not so easy, as the glandular capsule is thin and breaks easily. A thick layer of glandular tissue should have been allowed to remain in contact with the danger zone. Not only does it protect the patient against injury of the inferior laryngeal nerve and parathyroids, and save the surgeon great annoyance, but it has also a great cosmetic value; furthermore, if later another operation on the other lobe should become necessary, the chances for hypothyroidism will be greatly lessened.

*Resection is the method of choice* as it fulfils better than any other method all the requirements. This resection may be either *cuneiform* or *frontal*.

The *cuneiform* resection (Figs. 85 and 86) advocated in 1898 by Zoege von Manteuffel is made in the following manner: After the preliminary ligation of the superior or inferior thyroid arteries, or both together, the goiter is luxated; the imæ vessels are carefully tied, then an oval incision extending from the upper to the inferior pole is made into the glandular capsule and the parenchyma. The resection is then made by "wedging" out the interior of the gland. The amount of tissue removed by this "melon-slice" (Plate XIII) method is suited to the necessity of the case. Great care should be taken not to come too near the parathyroids and the inferior laryngeal nerves. The main bleeding vessels of the cut surface are caught and tied, then a continuous mattress suture of plain catgut through the glandular capsule, including a portion of the parenchyma, is made. (Plate XIV.) If the cup-shaped hole is quite deep, two rows of sutures may have to be made, one intraparenchymatous, and the other capsuloparenchymatous, which catches the edge of the capsule and rolls the two edges of the capsule into some semblance of a normal lobe. (Plate XIV.) Sutures should not be made too snug, as otherwise necrosis of the sutured portion might follow, especially if both main thyroid arteries have been tied. This method has the great advantage of leaving no exposed rough glandular surface afterward. Care should be taken to ligate every vein of the glandular capsule in order to avoid air embolism and postoperative oozing.

If the *transfrontal resection* is resorted to (Fig. 81), and this will be the method used in the majority of cases, it is done in the following manner: After having ligated the upper poles and starting at the upper pole, hemostats are placed all the way along the external border of the gland and then the parenchyma is cut. Next the operator proceeds from outward inwardly on a frontal plane, aiming to reach the lateral

PLATE XIII



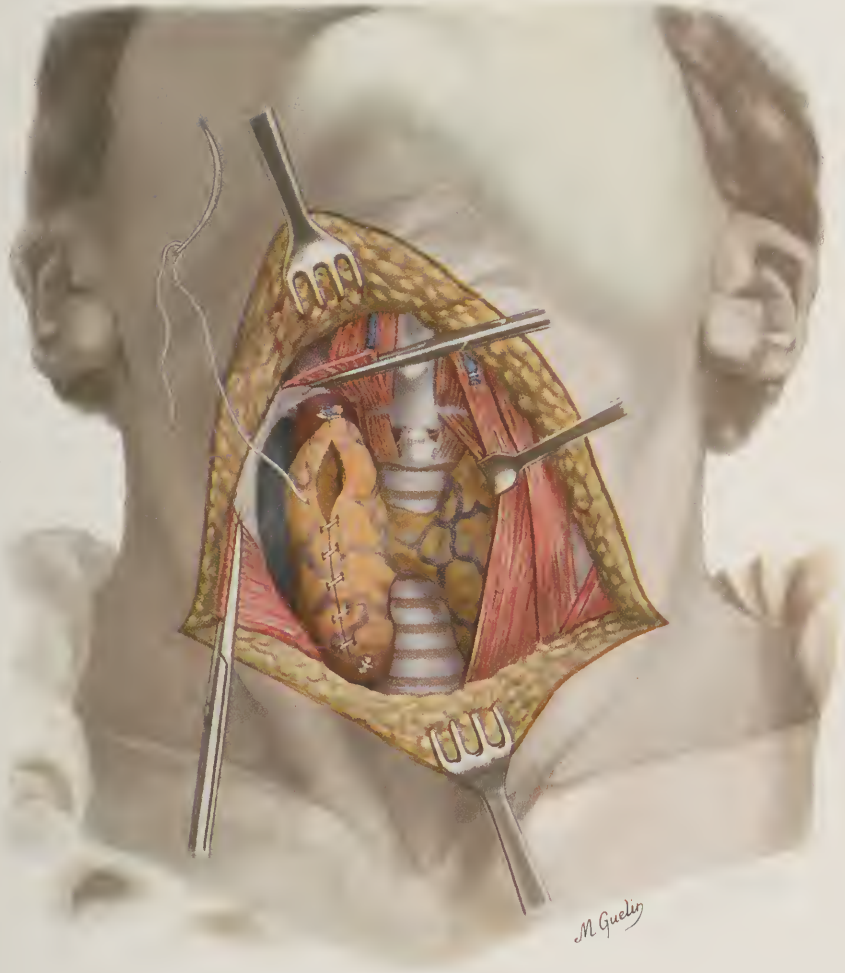
Technic of Cuneiform Resection.

The superior thyroid vessels have been tied, goiter luxated, and a "melon-slice" portion of the thyroid removed.





PLATE XIV



Technic of the Cuneiform Resection.  
The gland is then sewed up by continuous suture.



surface of the trachea, thus leaving a more or less thick glandular portion in contact with the danger zone. All the glandular tissue in front of the tractea, however is removed. The rough surface which remains after resection is completed, is left untouched; no effort is made to cover it by suturing the edges of the glandular wound together (Fig. 82). If however, one wants to suture the edges of the wound together as in Fig. 84 then resection must assume an angular form, the apex of the angle pointing directly posteriorly.

*Resection* will be employed in every case where a diffuse, parenchymatous enlargement, thyrotoxic or not, exists, and in all cases of diffuse colloid degeneration.

*Enucleation*, as such, has been discarded by the majority of surgeons, as it too often predisposes to relapses. They use this method in large, solitary, colloid and cystic goiters. In the majority of cases, however, enucleation will be combined with partial resection. In that case we shall call the operation *enucleo-resection*. Enucleation, however, should be given the preference over the resection method in the cases where the secreting parenchyma is reduced to a minimum. In such instances it is absolutely necessary to be as economical as possible with the glandular tissue, hence the indication to enucleate instead of to resect. When one has to be parsimonious with the thyroid tissue, it is better not to ligate the main vessels of the gland.

Enucleation finds its special indications:

1. In cases where there is a large but single cystic or colloid nodule.
2. In cases of complete colloid or cystic nodular degeneration of the entire gland. In such conditions a radical operation is not to be expected. The nodules are peeled out, one after another. There remain, of course, very small ones which cannot be enucleated, and which will be liable to relapse later on.
3. Enucleation can be employed, too, in cases of goiter which have relapsed.
4. If a nodular goiter takes its origin in the postero-internal region of the thyroid, it may, after it has reached a certain development, come in contact with the parathyroids and inferior laryngeal nerves. Enucleation in such cases is not without danger for these organs. Indeed, a hemostat put on a bleeding vessel, or a ligature, may injure the recurrent laryngeal nerves or the parathyroids. It is consequently better in such cases to leave a thin portion of glandular tissue in contact with the danger zone, even if that portion of the gland has undergone goitrous degeneration. Curiously enough, that portion of the goiter will revert to a normal state, and seldom will cause relapses.
5. When we have to deal with a multiple nodular goiter, *enucleo-resection* is the method of choice unless there should be some special

reasons to do otherwise, because if enucleation only is employed, the most of the intranodular thin bands of glandular tissue, which are still physiologically active, are caught in the sutures and ligatures and undergo fibrosis. Consequently the purpose for doing enucleation is defeated, hence it is better to combine it with resection.

The technic for enucleation is extremely simple. An incision is made over the glandular capsule and into the parenchyma, until the nodule is reached. This nodule is, as a rule, easily recognizable on account of its harder consistency, paler color, and diminished vascularization. The proper plane of cleavage is then sought; when it is found the nodule is peeled off very easily. The main thing is to start decortication only when one is certain to be in the proper plane of cleavage; as long as there is doubt, one can rest assured that the proper plane of cleavage has not been found. One does not need to fear the hemorrhage which takes place all over the entire surface of the shell left after the removal of the nodule, as it is mostly a parenchymatous hemorrhage. If, however, an artery of some consequence should bleed, the pouch can be everted and the bloodvessel clamped and ligated. Then a continuous purse-string suture starting internally at the bottom of the pouch brings its walls into close contact and *ipso facto* removes any possibility of any further hemorrhage. Finally, a continuous suture of the glandular capsule terminates the operation on the thyroid itself.

#### SHALL THE OPERATION BE UNILATERAL OR BILATERAL?

Shall the operation be *unilateral*, or *bilateral* as advocated by Mikulicz, Kausch and Halsted?

Of course this question applies only to the cases in which the thyroid is *bilaterally affected*. It would not enter into anyone's mind to advocate a bilateral operation unless there is a pathological reason for it on both sides. The question being so understood, I say, "Yes, the operation should be *bilateral* whenever it is *necessary* and whenever the *condition of the patient warrants it*, no matter if we deal with a simple or thyrotoxic goiter," despite the fact that Donald C. Balfour, in 1914, while pointing out the advantages of bilateral resection in simple goiter, said that its field of usefulness was very limited in the exophthalmic type. In the beginning of my surgical activity, I, too, was a devotee of the unilateral resection as practised by the majority of surgeons. But in following my own and other surgeons' cases, in which unilateral resection had been performed, I soon recognized the fact that this method was unsatisfactory, especially from an esthetic and relapse standpoint. Consequently, I gave it up and resorted to bilateral operations. Indeed, in bilateral pathological conditions of the thyroid this method is the only



logical one. Take, for instance, a multiple nodular goiter developed in both lobes. There is here really no sense in removing the goitrous nodules only on one side and leaving the others in the lobes, as these nodules are bound to grow and form another goiter. Sooner or later symptoms will reappear, and with them the dissatisfaction of the patient and the disappointment of the surgeon. From the esthetic point of view nothing has been gained by the unilateral resection, as one side of the neck is still puffed up, while the side where the operation has taken place shows a depression.

Let us consider a diffuse colloid degeneration of the entire gland. Here, again, why confine the surgical act to one side only? Even if a concomitant resection of the isthmus takes place, there still remains a diffuse, colloid degeneration in the other lobe. Here, again, the operation is insufficient; the functional as well as the mechanical disturbances have been only partly eliminated; the cure cannot be complete, relapses will occur. If such is the case why not resect bilaterally?

In dealing with a diffuse, non-toxic vascular goiter, the same reasons which have been invoked for resecting other goiters bilaterally still stand good. A bilateral resection should be done instead of leaving a large vascular parenchymatous goiter on one side.

But it is especially in the thyrotoxic parenchymatous goiter that bilateral resection finds its special indications. There, unless special contra-indications are present, the necessity for bilateral resection is an imperative one. In the great majority of cases one-sided lobectomy is insufficient to put a stop to hyperthyroidism. The patient is greatly benefited, yet not cured. The reason is because there is still too much thyrotoxic secreting gland left. Even ligation of the upper pole of the lobe left untouched is insufficient. That patient belongs to the class called by Kocher "*nicht fertig operiert*." Why not then from the start resort to bilateral resection? Functionally the results will be far better; esthetically they will be perfect.

Bilateral resection has the great advantage of affording a general view of the whole gland. This is indeed important. Despite the most careful and skilful clinical examination, who can be certain in every case before operation that a lobe is normal or not and to what extent it is damaged? Every surgeon has had, I am sure, the surprise of discovering at the operation only that a lobe which he considered as normal was not so, that a retrosternal goiter was present which had been unsuspected, etc. Furthermore, it is only after having inspected the whole gland that a surgeon can best decide how much gland can be resected on each side and what the nature of the technic will be, whether resection, enucleation or enucleoresection must be resorted to.

At first one might think that relapses must be, theoretically at least,

more frequent with bilateral resection than with unilateral excision. Indeed, with the latter method, the whole lobe having been removed, with the exception of a thin band of the posterior layer, relapse can hardly be expected, while, with the bilateral resection, as a thick portion of glandular tissue, normal or not, is left *in situ* the chances for relapse are greater. Consequently one might naturally conclude that unilateral excision is to be given the preference: goiter developing in the non-operated side must not be regarded as a relapse, but is a new goiter whose appearance cannot be charged to the method.

The argument retains, of course, its full strength whenever the lobe left untouched is normal. In that case if any goiter occurs, it must not be regarded as a relapse, but as a new growth. There cannot be any doubt about that. But in the great majority of cases things are not so: the pathological condition is not confined to one lobe only; as a rule both lobes are involved, one perhaps less markedly so than the other, nevertheless, they are both affected. Consequently that method is to blame which does not try to remedy the whole condition and which leaves purposely, knowingly, and carelessly, a goiter, no matter how small, on one side. An error of "omission" is, nevertheless, an error and should be charged with its consequence.

One thing has struck me very forcibly: it is the fact that after bilateral resection a diffuse parenchymatous or a colloid gland, toxic or not, has little tendency to relapse. It seems that after an operation the gland readjusts itself and reverts to the normal type.

Of course if the patient's condition is not good, if it is taking too great risk by resecting bilaterally, this operation must not be attempted; ligation of one, two, or three arteries should be given the preference; unilateral resection should be resorted to until the patient's condition warrants the attempt on the other side.

In conclusion we can say that:

1. *Bilateral resection is the method of choice*, whenever it is necessary and possible.
2. It affords a general view of the entire gland and does not let any goiter escape unobserved.
3. This method is much less apt to give relapse than the unilateral resection.
4. From an esthetic point of view it is ideal.
5. Technically the method is very simple. In fact, it is much simpler than the unilateral intracapsular excision and the risks of injuring the inferior laryngeal nerves and the parathyroids are certainly far less, provided, that a layer of thick enough glandular tissue is left in contact with the danger zone. The amount of hemorrhage is not materially larger than with enucleation or unilateral excision, provided pre-

liminary ligations of the main arterial trunks have been made, and provided, too, that the glandular tissue is cut only after being clamped with two hemostats.

6. When unilateral resection only is made, whenever there is a slight amount of thyrotoxicosis, or whenever bilateral resection must be deferred on account of the patient's condition, it is well to throw a ligation around the upper pole of the lobe which is left untouched.

### HOW MUCH THYROID TISSUE CAN SAFELY BE REMOVED?

From a purely physiological standpoint, and when dealing with entirely normal glands, it has been demonstrated experimentally by Colzi, von Eiselsberg, Fuhr, etc., that one-third or one-fourth of the entire gland, is sufficient to prevent myxedematous degeneration. Pineles found that one-eighth of the gland was sufficient to prevent thyroid insufficiency in the macacus. The remaining portion of the gland left *in situ* undergoes a compensatory hypertrophy which has been well described by Horsley and Halsted: cells begin to proliferate, become larger in size, and undergo a process of division forming new alveoli with colloid secretion.

It seems that every surgeon has his own rule. Von Eiselsberg leaves a portion of glandular tissue which can be compared in size to a hen's egg. Mikulicz leaves on each side a quantity amounting to the size of a walnut. Riedel is satisfied if he leaves one-tenth of the whole gland, while in bilateral goiters he leaves one-third of one lobe. Hoennicke, considering that the normal weight of the thyroid is in the neighborhood of 20 to 25 grams, makes it a point to leave *in situ* enough gland to equal about this weight. De Quervain leaves enough thyroid tissue so as to equal the volume of the normal thyroid gland. Kocher claims that whenever the thyroid shows a diffuse parenchymatous degeneration one-fourth of the total volume of the gland should be left *in situ*. Mayo says that an entire lobe, the isthmus and the two lower thirds of the other lobe, can be safely removed. Kausch leaves one and one-half times the size of the normal thyroid. Hunnicutt found that one and three-fourths of a dog's thyroid gland may be removed without affecting the remainder of the gland and that compensatory hypertrophy, claimed by Halsted to exist after removal of the gland, does not take place.

It is obvious that these more or less theoretical rules cannot be applied to every case, as it would be erroneous to believe that a certain amount of pathological glandular tissue has the same physiological power as an equal amount of normal thyroid tissue. It is consequently wrong to set down a uniform rule which should be applied in every case. It is obvious, too, for instance, that if a patient with diffuse col-

loid goiter shows symptoms of hypothyroidism, this thyroid insufficiency is bound to become more marked after a certain portion of the gland has been removed. It would consequently be a mistake to remove in such cases as much thyroid tissue as in a case of hyperthyroidism, for instance. In the former case all that we want is to relieve the patient of his pressure symptoms, and to relieve him of his deformity, but we should have constantly in mind the necessity of leaving as much thyroid tissue as can possibly be done, whereas in the latter case the functional activity of the thyroid being what we are trying to diminish, we shall feel at liberty to remove a far greater amount of thyroid tissue than in the former case. Furthermore, it should always be borne in mind that a certain amount of glandular tissue left after the operation undergoes resorption on account of the vascular disturbances and the organization of the blood clots and the connective-tissue formation due to the sutures. This should be taken into consideration when deciding how much tissue should be left. One might expose himself to disappointment if he should count too much on the so-called "compensatory hypertrophy" of the remaining portion. Halsted seems to be presently inclined to believe that this compensatory hypertrophy is only a process of reaction of the thyroid to a low-grade infection.

We may consequently conclude:

1. In simple goiter, colloid or cystic, multinodular or not, without hypo- or hyperthyroidism symptoms, enough thyroid tissue should be left on each side so as to equal about the volume of one-third to one-half of a normal lobe.
2. If hypothyroidism symptoms are present, the amount of tissue left must be in proportion to the degree of hypothyroidism and may equal two or three times the size of the normal lobe on each side.
3. In hyperthyroidism to leave an amount equal to one-third to one-fifth of a normal lobe is a safe procedure.

#### SHALL WE DISSECT THE PARATHYROIDS?

Some surgeons have thought that they would avoid injury to the parathyroids by dissecting them *in situ*. *A priori* this is rational, but the results obtained have not been encouraging. Indeed, when dissecting a cadaver, if we stop to think how difficult it is sometimes to identify these little bodies, how little they differ from a small accessory thyroid glandule, from small lymph glands, or even from small fat nodules, it will then be easily understood why the above-mentioned method is impractical. It would necessitate a prolonged, tedious, and often an unsuccessful operation; it would expose, furthermore, to troublesome hemorrhages by injuring the numerous veins of that region and



would have too often as a result, the injury of the organs which we are trying to protect, namely, the inferior laryngeal nerves and the parathyroids. It is quite plain that these disadvantages and dangers add to those of a prolonged operation. Consequently, any method whose aim would be to identify *de visu* these little too often hypothetical organs is bound to be unsatisfactory. It must then be discarded. The best way not to injure the parathyroids is to ignore them by leaving them undisturbed with the posterior capsule.

### LIGATIONS.

The ligation of the thyroid arteries in goiter was already utilized by veterinary surgeons for goiters of horses, and was proposed as a therapeutic measure in human surgery by von Muys in 1639 and Langhe in 1707. The first ligation in man was done by Blizzard in 1813, when he tried to ligate the superior thyroid artery in order to cause the atrophy of a large goiter. The patient died from hemorrhage. In 1814 Walter attempted this operation again and succeeded. The ligation of the inferior thyroid was done for the first time by Porter in 1852, but it was only in 1888 that Wölfler and Rydigier applied this method systematically to goiter surgery. They obtained good success especially in the vascular and parenchymatous forms. In cancerous, cystic, fibrous and calcareous forms the method failed, as could be expected, to give satisfaction. Later, when the technic became better worked out and the antiseptic era protected the patients against infection, these ligations were given up and replaced by thyroidectomy. Today they are used only as a preliminary step to thyroidectomy in Basedow's disease.

The vasomotor and secretory nerves of the thyroid penetrate into the thyroid by the same route as do its bloodvessels. At the upper pole small branches of the *external laryngeal nerve*, which itself is a branch of the vagus, penetrate into the gland with the superior thyroid artery as well as the sympathetic branches. At the inferior pole the nervous branches reaching the thyroid gland in conjunction with the inferior thyroid artery are mostly all of sympathetic origin. According to Briau these branches come from the superior middle and inferior cervical sympathetic ganglions and anastomose freely with the cardiac nerve branches of the vagus. It is found that the inferior laryngeal nerve sends directly to the thyroid gland a very few small fillets whose physiological action is not known.

It is a very well-accepted fact today that the branches of the superior laryngeal penetrating the thyroid at its upper pole are essentially *vasodilatatory*: this has been demonstrated plainly by Frank and Hallion.

More so, according to Ascher-Flack (*Centralblatt für Physiologie*, June, 1910, xxiv, 211-213), the irritation of the peripheral end of this nerve produces an increased secretion of the thyroid; consequently the external superior laryngeal is not only a vasodilatatory, but is also at the same time an excitosecretory nerve. The central irritation of the depressor nerve causes an intense vascularization of the thyroid through a reflex intermediary action of the external laryngeal nerve. The action of the sympathetic branches are, according to Frank, Hallion and von Cyon, vasoconstrictory. Their division causes, according to Missiroli (*Archivio di fisiologia*, 1908, vi, 582-594), a hypersecretion of the thyroid parenchyma. If this is really so, then sympathectomy for Graves's disease is illogical; at any rate some other explanation should be given in order to explain its favorable results in that condition.

In the light of the above considerations it follows that with our ligations we not only diminish the blood supply of the thyroid gland, but also, at the same time, we deprive, to a certain extent at least, the thyroid of its nerve supply. In fact, our ligations should be considered as true angioneuromotomies.

If we sum up these facts and the ones spoken of in the chapter on the Blood Supply of the Thyroid, we come to the following conclusions:

1. With our ligations we not only diminish the blood supply and consequently the secreting power of the thyroid, but we act directly upon the gland itself by determining atrophy of the territory deprived of the blood circulation. This atrophy is in direct proportion to the amount of blood supply suppressed. It causes a thickening of the capsule and an interstitial cirrhotic process invading the gland throughout; the epithelial elements have the tendency to revert to their normal type.

2. Since the external laryngeal nerve has a marked vasodilatatory and excitosecretory action upon the thyroid, and since the sympathetic branches penetrating the thyroid with the superior and inferior thyroid arteries seem to be less important physiologically, it follows that our efforts should be directed against the external laryngeal nerve. This can be done easily at its point of entrance into the gland, namely, at the upper pole, by performing a ligation including all the branches of division of the superior thyroid artery. In so doing all the branches of the external laryngeal nerve are bound to be caught. This is best done by the *polar ligation method* of Stamm and Jacobson. This ligation must be double, and in order to be most effective, the neurovascular pedicle included between the two ligatures must be severed with a knife or scissors. In that way the branches of the external laryngeal are surely divided. The ligation then becomes an angioneuromotomy.

3. Whenever the condition of the patient is such as to warrant a ligation only, the ligation of the superior pole is the method of choice,

because to the suppression of the vascular supply we add the suppression of the nervous supply through the external laryngeal nerve.

4. If the condition of the patient warrants a double ligation, the ligation of the superior pole and of the inferior thyroid artery on the same side is the method to be chosen. Indeed, as the anastomoses between the inferior and superior thyroids are very numerous, whereas the bilateral anastomoses are very much less developed, the maximal effect will be obtained if we obliterate the thyroid arteries of the same side instead of ligating, as is so frequently done, both superior arteries.

5. For the same reasons, if the upper pole has been previously ligated the one which will have to be ligated next will be the inferior thyroid on the same side.

6. If three ligations are performed in one or several sittings, two must be performed on the same side, and the third on the upper pole of the opposite side, so that there will finally remain one thyroid, the inferior, to ligate if one chooses to do so.

7. Ligation of the four thyroid arteries in one or more sittings can be done without danger of necrosis of the thyroid gland and without danger of tetany, unless vascular anomalies should exist, and this cannot be foretold.

**Indications for Ligation.**—One of the greatest advocates of this method of treatment of Basedow's disease was Kocher. As he said: "If we ligate one artery only, we obtain an amelioration of the patient's condition; if we ligate two arteries the amelioration is greater; if to it we add the removal of one lobe, the amelioration is still greater. If the results obtained are not sufficient, we can ligate one or two arteries on the other side, and we can perform another partial thyroidectomy on the lobe which has not been touched." These views have since been almost universally accepted by the majority of operators. *In advanced cases successive and graduated operations are the method of choice.* Ligation alone of two or three, or even of four arteries, will very rarely suffice to cure the patient who is seriously ill with Graves's disease. Although considerable improvement may follow, thus allowing the surgeon to perform a more radical operation, a complete and permanent cure is hardly to be expected. *Ligations must always be practised with the view of improving the patient's condition so as to allow a thyroidectomy to be safely performed later.* These small operations have the further advantage of testing the patient's resistance to the operation; they consequently give precious indications for the future surgical procedures. If it is true that whenever safely possible, it is better to resort to thyroidectomy at once without preliminary ligations, ligations must be reserved for those thyrotoxic cases where thyroidectomy cannot be safely undertaken.

In that I differ radically from the surgeons who advocate the ligation

of the four thyroid arteries instead of resection of the thyroid gland. In my judgment, if a patient is able to stand the ligation of the four arteries in one sitting, there are ninety-five chances out of one hundred that he is able to stand the bilateral resection. The time consumed, the surgical shock, and the danger to the patient will not be greater in performing the bilateral resection than in ligating the four arteries in one sitting. The few times that I have resorted to the four ligations in one sitting, were when I was in doubt about the patient's ability to go through the ordeal. In every instance, however, I felt afterward that the patient would have stood the resection as well. We all admit that, in the last analysis, resection is the ultimate aim whenever one wants permanent results.

Ligations are clearly indicated in those forms of non-toxic vascular goiters in which the essential feature is an enormously increased vascularization. Here the goiter resembles an angioma cavernosum with all its vascular symptoms, abnormally marked blood supply, thrill, systolic murmur, partial reductibility by compression, etc. Thyrotoxicosis may be totally absent. This is the *struma vasculosa* of Kocher. Ligations in these forms of struma can be performed in one sitting and can be applied to the four arteries. A complete cure may be hoped for by this simple method.

Ligations are ordinarily not indicated for the secondary forms of Graves's disease, namely, in Basedowified goiters. In these cases their efficacy is only slight, and the same is true for the non-toxic parenchymatous goiters. Exceptionally, however, if in certain severe Basedowified goiters not safely justifiable at once of thyroidectomy, the vascular symptoms should be very pronounced, preliminary ligations may be very beneficial, as they diminish the blood supply, and what is of utmost importance, lessen the thyrotoxic symptoms.

There are cases of Basedow's disease apparently of nervous origin and characterized clinically by the absence, or almost absence, of thyroid physical symptoms. The symptom-complex seems to take apparently its origin in an intense irritation of the cervical sympathetic system. In these cases ligations, and even resections, are not satisfactory. Resection of the sympathetic nerve with one or two of its ganglia seems to be, for the time being, the method of choice.

It is wiser to discharge a patient after ligation and to instruct him to return for operation six to fifteen weeks later, because, when the patient returns he is in far better condition to stand the surgical ordeal than if he had been kept in the hospital all that time. Although in a great many cases the improvement after a ligation continues for several months, as a rule, this improvement is not permanent and relapses are very likely to occur. Under such conditions the benefit of the ligation is lost and resec-



tion of the gland becomes as dangerous as if ligation had not been performed.

When the patient returns, if thyroidectomy is still considered unsafe, a second, a third, even a fourth ligation may become necessary before thyroidectomy may be undertaken. From three to five months are then permitted to elapse in order to give the patient a chance to get the full benefit of these operations. Only then, and that is if the condition of the patient warrants it, may thyroidectomy be performed; otherwise the fourth artery should be ligated. In cases of advanced thyrotoxicosis in which the organs have undergone a secondary change, such as nephritis, hepatitis, myocarditis, arrhythmia, etc., the dangers of an operation, whatever it might be, ligations or resection, are quite great, and the hope for cure, or of great improvement, is only slight.

**What is the Point of Election for Ligation?**—For the *superior thyroid artery* there is no discussion. This ligation takes place just before its entrance into the upper pole. It is best done by the polar method of Stamm and Jacobson. (Plate XV, Fig. 3.)

For the *inferior thyroid artery* divergences of opinion still prevail. Some surgeons advocate ligation at its point of entrance into the glandular capsule; others advocate the ligation just inwardly of the vascular cord; while others advocate ligation at the inner border of the scalenus anticus.

Ligation of the inferior thyroid artery *near its point of entrance into the thyroid* has many disadvantages. It necessitates, first, the dislocation of the goiter. This is by no means always easy. In exophthalmic goiter, hemorrhage from the goiter itself occurs easily during this act, on account of the adhesions with neighboring tissues, and because of the friability of the bloodvessels. Furthermore, since the search for the artery takes place in the perithyroidal cellular space, which we know is very vascular, this search for the artery or its branches in that region is rendered difficult by the numerous veins found, whose injury increases the difficulty of the operation. Furthermore, we must not forget that this region constitutes the *danger zone* (Plate XI, Fig. 2), which must be absolutely avoided, unless one wishes to run the risk of injuring the inferior laryngeal nerve and the parathyroids. In addition to this, at that level, the inferior thyroid artery has, as a rule, already undergone division into several branches so that one often ligates only a branch instead of the main trunk; the small parathyroid artery in that region is bound to be injured, and the parathyroids and the inferior laryngeal nerve are so interwoven with the branches of division of the inferior thyroid artery that the risk of injuring them is great. (Plate XI, Fig. 2.) In the light of all these considerations ligation of the artery near its point of entrance into the thyroid is not to be advocated. The same is true for the *intra-*

*capsular ligation*, practised by those who perform thyroidectomy by the decortication method. The same is true for the "ultraligation," as advocated by Halsted.

The point of election for ligating the inferior thyroid is *inwardly of the carotid sheath*, soon after the artery has crossed it transversely and posteriorly. (Plate XI, Figs. 1 and 2.) In many instances the thyroid is so hypertrophied that its lateral border overlaps the vascular cord. Ligation of the artery at that point consequently offers, in the opinion of Delore and Alamartine, the same dangers and disadvantages as if the artery were ligated at the point of entrance into the thyroid. They, for this reason, consider the ligation of the artery at the inner border of the scalenus anticus as the method to be followed. (Plate XII, Figs. 1 and 2.) These conclusions seem to me not quite correct. To be sure, sometimes the thyroid is so enlarged as to render this ligation very difficult. I grant that in these cases the method for the ligation of the inferior thyroid is the one they propose. This, however, is not common. As a rule, even with voluminous thyroids, it is possible to retract the carotid sheath outwardly and the thyroid inwardly so as to allow ligation to take place without too great difficulties. If luxation of the goiter can be performed, then ligation of the inferior thyroid can surely take place at the point of election. It should not be forgotten that in undergoing enlargement the thyroid gland does not carry with it and away from their normal places the parathyroids and the inferior laryngeal nerves. These organs remain where they are, no matter how large the goiter may become, whereas the carotid sheath is displaced laterally and posteriorly, so that in reality the ligation of the artery just inwardly of the vascular cord does not expose these organs to injury. Another advantage of ligating the inferior thyroid artery at the point of election as just mentioned, is that at that point ligation takes place outside of the perithyroidal cellular space. This lessens the danger of injuring the veins which are usually found in it. For all these reasons we may conclude that the point of election for the ligation of this thyroid artery is *just inwardly of the vascular cord*. (Plate XXIII.)

In ligating the artery at that point injury to the inferior laryngeal nerve and to the parathyroids is quite out of the question. Furthermore, the danger of injuring the veins of the perithyroidal cellular space is practically *nihil*. The only organ which might be injured is the sympathetic nerve with its middle cervical ganglion. In the light of our modern views, even if such a thing should happen, the patient would not be the worse for it. I even think that in many instances, inasmuch as the sympathetic lies just behind the artery imbedded in areolar tissue, it is a good plan to add to the ligation the resection of the sympathetic nerve. That is precisely what I sometimes do.

## PLATE XV



FIG. 1.—The skin and platysma myoides have been cut. The omohyoid and sternohyoid muscles are then encountered. They are divided bluntly at their point of junction. The division of these muscles follows the same direction as their muscular fibers.

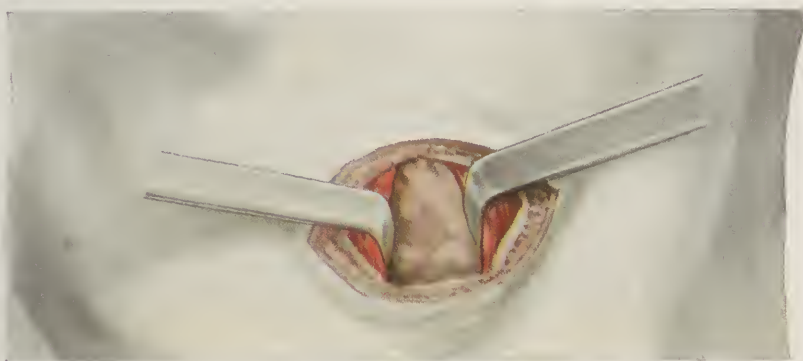


FIG. 2.—The upper pole of the thyroid is then isolated.



FIG. 3.—A curved thread carrier is swung around the upper pole and ligation is made so as to bite off a little of the thyroid tissue. Another ligation is placed a little above and the thyroid vessels are then cut between the two ligatures.

Figs. 1, 2 and 3.—Ligation of the Upper Pole.





**Technic of Ligations.**—The problem whether general or local anesthesia should be used is one to be decided with each individual case. On the condition of the patient depends, too, how many ligations should be done in one sitting.

The polar ligation of the superior pole is, as a rule, an easy operation and quickly done. I have often performed it while the patient was still in bed, in order to reduce to a minimum the amount of fear and shock. But the ligation of the inferior thyroid is a more complicated matter because it is of more difficult access. Some authors even claim that this operation is as serious as thyroidectomy itself. In the great majority of cases, however, this assertion is certainly exaggerated.

Ligation of the four thyroid arteries in one sitting should seldom be made, because if the patient's condition is such as to warrant a ligation of the four arteries at the same time, thyroidectomy should by all means be preferred to ligations. The amount of fear and shock will not be greater, and the result will be far more satisfactory and permanent. However, if one should choose to do so, either because he has to deal with a struma vasculosa, or for any other reasons, then the transverse, or low-collar incision, made in the usual way for thyroidectomy, should be given the preference. It is better to expose the gland in a similar manner just as if thyroidectomy were to be performed; the two upper poles are dissected out and ligated. The same is done for the inferior thyroid arteries on both sides.

**Isolated Ligation of the Superior Pole.**—A transverse or slightly oblique incision of four or five centimeters is made laterally to the thyroid cartilage at the level of its superior border, and if possible, in a skin crease. As in the large majority of cases the superior pole is easily felt, the latter may serve as a landmark for the place where the incision must be made. The two skin flaps are retracted; a small branch of the superficial cervical plexus and one of the anterior jugular veins may be encountered. They are retracted. The omohyoid and sternohyoid muscles are then prepared and separated bluntly in the direction of their running fibers. (Plate XV, Fig. 1.) The fibers of the sternothyroid, which lie underneath, are divided longitudinally, bluntly too, and well retracted with blunt hooks. The upper pole is thus brought into view. (Plate XV, Fig. 2.) It is prepared, doubly ligated with silk carried by a curved ligature carrier, and cut between the two ligatures. (Plate XV, Fig. 3.) One should always have in mind that it is not by any means difficult to miss the dorsal branch of the superior thyroid artery while passing the ligature around the upper pole. This fact may sometimes account for the failure to realize an expected improvement in a patient with a toxic goiter after unilateral or bilateral ligation of the upper pole was thought to have been accomplished. No drainage; one or two separate sutures for the muscles; suture of the platysma and intradermic suture.

**Technic for the Isolated Ligation of the Inferior Thyroid Artery.**—Precisely in the line of the transverse incision, contemplated for future thyroidectomy, and over the tendon of the omohyoid muscles, a transverse incision of 6 to 8 cm. is made. The two skin flaps are retracted upward and inward. Just along the inner border of the sternocleidomastoid muscle and parallel to it an incision is made on the fascia covering the prethyroid muscles (Plate XVI); then the finger penetrates bluntly between the sternocleidomastoid and the prethyroid muscles so as to

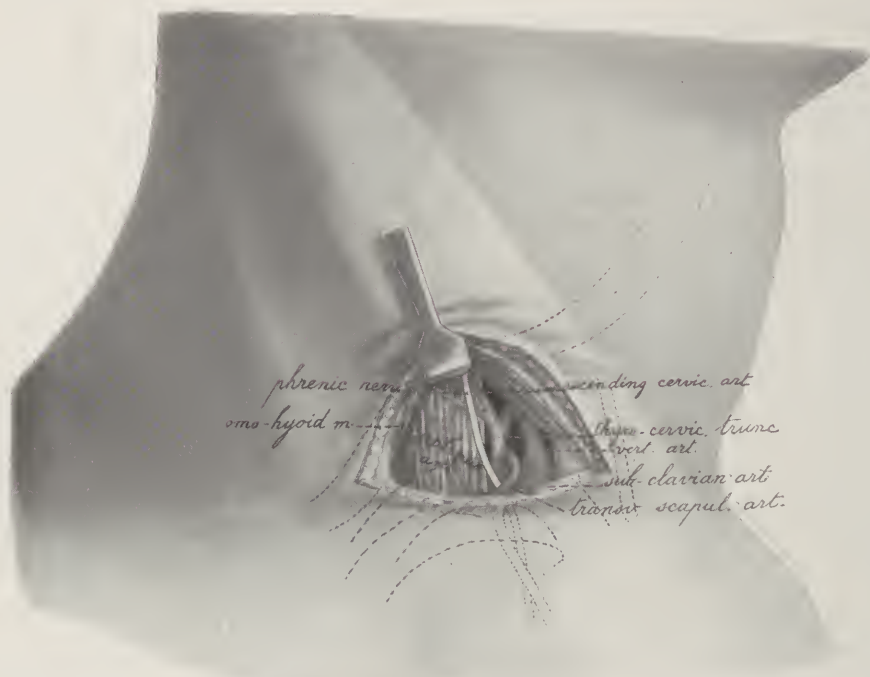


FIG. 87.—Ligation of the inferior thyroid artery. Incision is made above the clavicle in order to penetrate the triangle formed by the sternocleidomastoid, omohyoid and the clavicle. The thyrocervical axis is then located and the inferior thyroid tied. Note the close relation of the phrenic nerve to the thyrocervical trunk.

travel through the sternocleidomuscular plane of cleavage until the carotid sheath is located. The sternocleidomastoid muscle and the vascular cord are then retracted laterally and the thyroid gland covered with its prethyroid muscles is retracted inwardly by a retractor especially designed for the purpose. (Plate XVII.) Great care should be taken not to open the surgical capsule of the thyroid. A finger then goes in search of Chassaignac's tubercle or the anterior tubercle of the transverse process of the sixth cervical vertebræ. One centimeter below this tubercle, as a rule, the inferior thyroid artery is found, its pulsations

PLATE XVI



Ligation of the Inferior Thyroid Artery.

This operation is supposed to be a preliminary step before attempting thyroidectomy, hence the large incision made. The superficial cervical fascia has been divided just in front of the sternocleidomastoid muscle. This muscle is retracted outwardly while the prethyroid muscles and the thyroid gland are retracted inwardly. (The picture shows a portion of both anterior jugular veins missing. This is an error.)





PLATE XVII



Ligation of the Inferior Thyroid Artery.

The sternomastoid and the muscular capsular space have been entered. The carotid sheath is then retracted outwardly while the prethyroid muscles and the thyroid gland are retracted inwardly. The surgical space is carefully avoided. The inferior thyroid is then located and tied.



facilitating the finding of it. A curved blunt thread-carrier with a small radius is used to carry the ligatures. Care should be taken in handling this artery, as it is often thin and friable, and especially so in Basedow's disease.

Sometimes the artery is not found. It may be caught by the assistant's retractors and compressed so as to prevent its pulsations being felt, but release of this pressure will soon tell as to its presence. If at the point where the inferior thyroid is supposed to be, instead of finding an artery with a transverse direction, one with a vertical direction is found, then we have to deal with either the truncus thyreocervicalis or with the ascending cervical artery. This is a precious indication, as it will help to find the inferior thyroid artery. If, however, these researches fail the conclusions must be reached that very likely this artery is absent.

**Isolated Ligation of the Inferior Thyroid on the Inner Border of the Scalenus.**—Dietrich and Langenbeck, who were the first to advocate this method, used to pass between the two heads of the sternocleidomastoid muscle. Drobnik, Rudigier and Wölfler have advocated the following method (Fig. 87):

Two centimeters above the clavicle and about 0.5 cm. behind the posterior border of the sternocleidomastoid muscle a slightly upward-curved incision of 5 cm. is made. The superficial cervical fascia is divided and if the external jugular vein is encountered it is clamped and cut. In the triangle formed by the sternocleidomastoid muscle the omohyoid and the clavicle a blunt dissection takes place until the scalenus anticus is found. On its anterior surface lies the phrenic nerve: it is retracted inwardly with the fat tissues. On the inner border of the scalenus the inferior thyroid is felt pulsating and may also be seen. It is ligated between the two ligatures and cut. No drainage; intradermic suture. This operation has the great advantage of taking place far from the thyroid gland and its danger zone. It causes no risks of tetany, of injury to the inferior laryngeal nerve or of hemorrhage through injury of the thyroid vessels, but it necessitates a new incision, and hence another scar.

**Hemostasis.**—Hemorrhages were for a long time a feared complication of goiter operation. With our present anatomical and technical knowledge, however, this complication can now be avoided almost entirely. Of course, there will always be operations in which hemorrhages, no matter what is done, will be abundant; especially in Graves's disease, where, because the bloodvessels are thin and friable, hemorrhage is sometimes quite marked despite a good technic. There will always be, too, hemorrhages due to some unexpected and unavoidable accident. These complications, however, can be reduced to a minimum.

Hemorrhages may be: 1st, arterial; 2d, venous; 3d, parenchymatous.

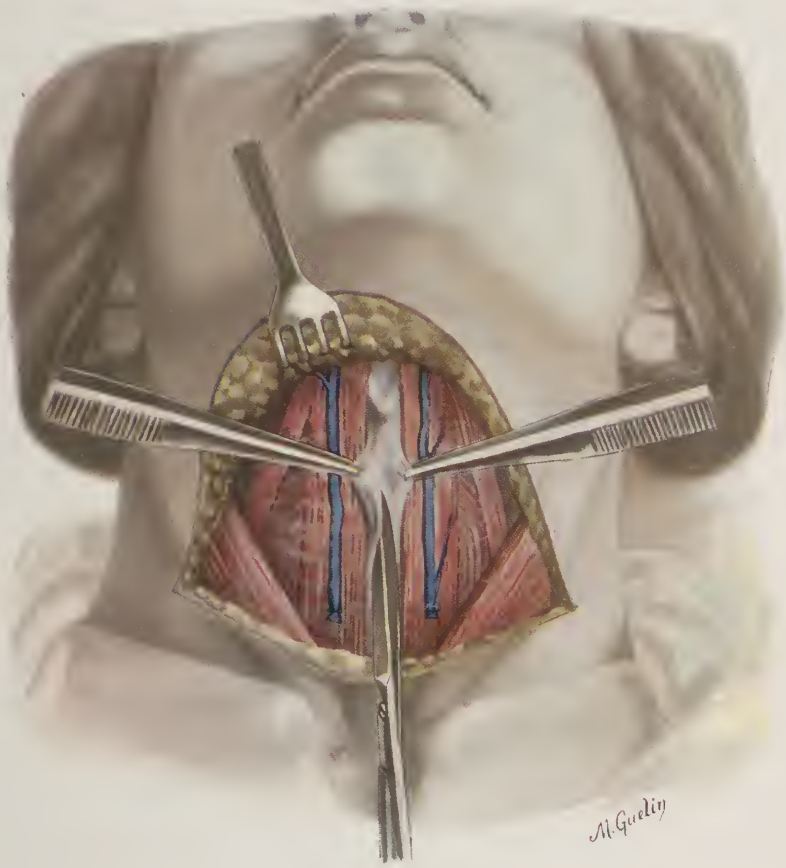
Despite unilateral ligation of the superior and inferior arteries and veins of the thyroid, we know from our own previous studies that hemorrhage may still occur on account of the bilateral anastomoses and collateral circulation from the neighboring tissues. Parenchymatous hemorrhage is, as a rule, of little importance. In certain very vascular goiters, however, the hemorrhage may be so diffuse and so abundant that one hardly knows where to put a hemostat. Furthermore, the parenchyma and vessels may be so friable that any attempt to place a hemostat or a ligature only results in an increase of the hemorrhage. The only and the best way to stop this diffuse parenchymatous oozing is to use what the French authors call the "ligature en masse." This is done by including in the ligature a certain amount of glandular tissue and by tying the ligature just tight enough to stop the oozing, but not to break the glandular tissue.

Hemorrhage can be greatly reduced if one follows the following rule: Never cut the glandular capsule and the parenchyma unless previously clamped, and then operate carefully, anatomically and systematically.

By ligating the one or two thyroid arteries prior to undertaking resection of the gland, hemorrhage may be reduced to a minimum. The preliminary ligation of both the superior and inferior thyroid arteries, prior to resecting the goiter, is not considered by everyone as a necessary step to the operation. In Kocher's, De Quervain's and many other surgeons' work, ligation of both the superior and inferior thyroid arteries is a part of their technic. On the other hand, Mikulicz, Kausch and others do not strive to do so. Kausch, for instance, ligates the superior thyroid only: he is never concerned with the inferior thyroid. I share the same views, except when I have to deal with thyrotoxic goiters in which the diminution of the blood supply of the remaining glandular portion is one of the aims of the operation. Otherwise, in ordinary simple goiters I really do not see the necessity for ligating the inferior thyroid before removing the goiter. On the contrary, I consider that leaving the inferior untouched is one of the best assets for the vitality of the remaining glandular portion, and especially for its functional activity. It is rare that hemorrhage during operation is such that the only means to check it is to add to the ligation of the superior thyroid artery, the ligation of the inferior thyroid. Another reason for giving up the ligation of the inferior thyroid is to avoid any chance of injuring the inferior laryngeal nerve and the parathyroids. Furthermore, quite often the vitality of the remaining portion of the gland is already reduced, and consequently if it is further lowered by shutting off its main blood supply, it will hardly be able to take care of the ligatures' material, and especially so if the



PLATE XVIII



Thyroidectomy.

The low-collared incision being performed and the two skin flaps retracted, the prethyroid muscles are divided in the middle line.



PLATE XIX



Thyroidectomy.

The operator then goes with the index fingers into the musculocapsular space, thus loosening the prethyroid muscles away from the gland.





latter is non-resorbable, hence pus and elimination of the threads. On the other hand, as a routine measure, I always ligate the superior pole before starting the resection.

It is scarcely necessary to state, if ligation of both superior and inferior thyroids is attempted by the surgeon as a part of his routine technic, since this ligation has for its sole object the reducing to a minimum of the hemorrhage during the surgical act, that it should take place before beginning the resection of the gland. This again is not viewed by everyone in the same way: I have often seen surgeons performing this ligation after the removal of the goiter was terminated. At that time of the operation, this ligation is, in my judgment, entirely unnecessary, as it presupposes that hemorrhage has already been mastered. Indeed, in the great majority of cases, as soon as the goiter has been removed, hemorrhage diminishes in a surprising manner: a few hemostats here and there and the bleeding is controlled. Once in a great while, however, the oozing is so profuse that it seems more expedient to resort to the ligation of the inferior thyroid artery in order to check the bleeding. This, however, is rare. At any rate, if one believes in the necessity of ligating the inferior thyroid artery, the only logical moment to perform it is before starting the resection of the goiter itself. As said before, exception can be made for thyrotoxic goiters. In these cases, if for some reason ligation of the inferior thyroid artery has not already been done, it can then take place after the goiter is removed.

## CHAPTER XLI.

### OPERATIVE TECHNIC FOR THYROIDECTOMY.

#### INCISION.

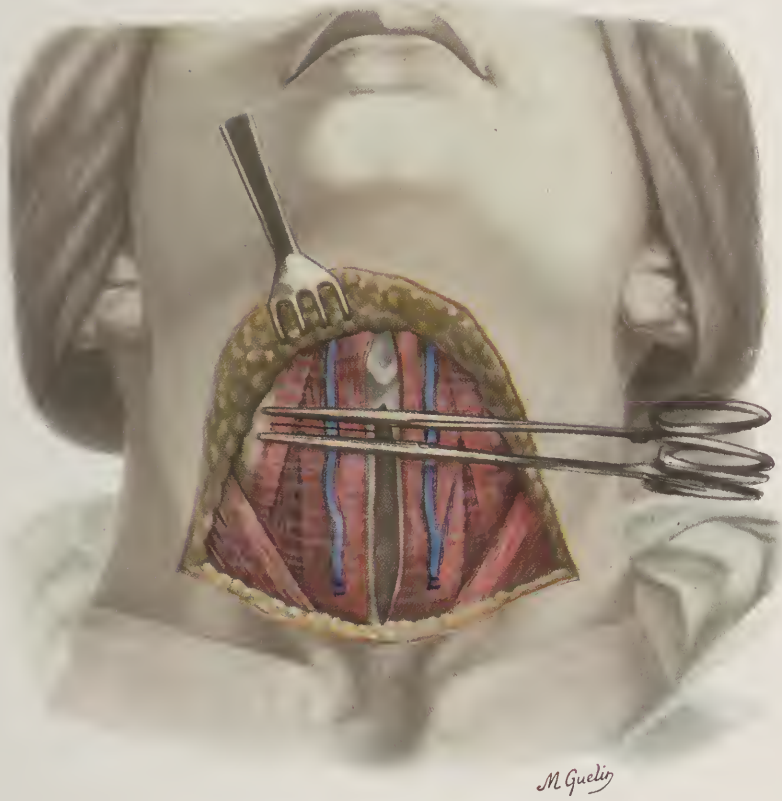
1. IN the greatest number of cases the incision of choice is the *low-collar* incision of Kocher. It is the one which certainly gives the best cosmetic results and when properly placed allows the surgeon to perform every step of the operation without difficulty. It is slightly curved, its concavity being directed upwardly; it should be perfectly symmetrical. The incision is made one or two centimeters above the manubrium sterni. The length varies, of course, with the size of the goiter. The fault too often made by beginners is that of a small incision. In larger goiters the incision extends from the middle of one sternocleidomastoid muscle to the other, or better said, from one external jugular vein to the other. In the average case it can be made much smaller. If local anesthesia is used, the incision must be larger than with general anesthesia so as to diminish the pain caused by the necessary pulling upon the retractors. It is better to give the preference to a slightly curved incision than to a straight transverse cut. In unusually large goiters the esthetic side may have to be disregarded; the "Winkelschnitt" of Kocher or angular incision with well-rounded angles above the cricoid cartilage will then give far better access to the tumor than any other incision. This incision, however, will seldom find employment because very large goiters are becoming more and more rare every day, and because, too, a well-arched collar incision will almost always meet every demand.

Other incisions are sometimes advocated as the "H," "T," and "U" forms. They only prove that the surgeon who uses them is not very much concerned with the esthetic side of his work. These incisions will soon have only an historical interest.

2. The subcutaneous tissue and platysma are then retracted, the upper flap as high as the thyroid cartilage, the lower flap to the episternal notch. (Plate XVI.) The two median and oblique jugular veins are clamped and cut; the two external jugular veins are left uninjured. The upper and lower flaps are maintained retracted either by an automatic retractor or by an assistant.

3. A vertical incision extending from the thyroid cartilage to the episternal notch is made in the middle line between the prethyroid

PLATE XX



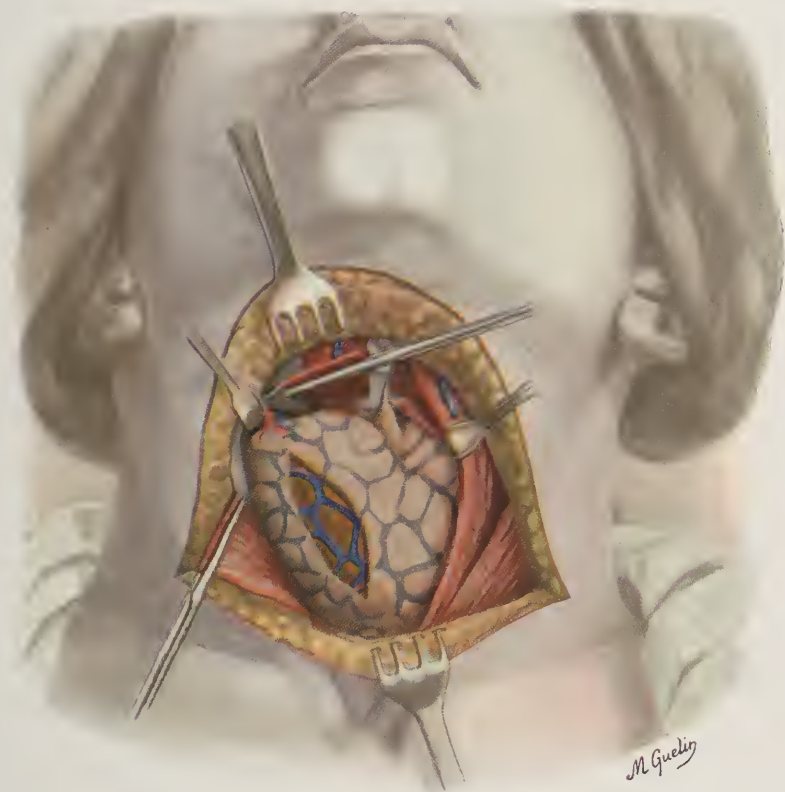
Thyroidectomy.

When necessary the prethyroid muscles are divided at their superior ends after being clamped between two hemostats.





PLATE XXI



Thyroidectomy.

The goiter is thus fully exposed. The surgical capsule is then opened so as to allow the surgeon to enter the proper plane of cleavage, which is the surgical space.



muscles. (Plate XVIII.) A finger is then introduced under them and going up and down, loosens their posterior surface as far up and down as possible. (Plate XIX.) The greater amount of pressure must take place anteriorly against their posterior surface so as to avoid injury of the subjacent veins.

4. For moderately sized and non-complicated goiters the mere lateral retraction of the prethyroid muscles affords sufficient access to the field of operation. In few instances, however, it becomes necessary to cut them transversely. (Plate XX.) The point of election for their section is at their upper end; in that way their nerve supply is not injured while the section breaks the line of scar, thus preventing the muscular suture from becoming adherent to the cutaneous one. These muscles are clamped transversely and cut between parallel hemostats, on one or both sides according to the necessity, and are retracted laterally and downward. Furthermore, these muscles are treated as one structure technically throughout the operation, and are always manipulated as one object; they are not being freed of their fascia covering them. Usually, however, the omohyoid muscle does not need to be cut. The time lost in liberating, clamping, cutting, retracting, and sewing up these muscles when the operation is done is practically not worth mentioning. At any rate, it is more than sufficiently offset by the ease, rapidity and safety with which the operation can be done, and by the minimum of traumatism inflicted upon the patient.

The sternocleidomastoid muscle does not need to be incised at all. Its lateral retraction is sufficient to give plenty of access to the field of operation. It may, however, become necessary in large intrathoracic goiters to cut temporarily its sternoclavicular insertion. In that case its two ends must be sewed up afterward.

5. There is no need to say that, as the operation is progressing, every bleeding-point is at once blinded with hemostats which are left in place or removed after immediate ligature has been made. In a most general way, but especially when dealing with the gland itself, clamping with hemostats must always be done before cutting and not afterward.

6. The surgical capsule is now open and the glandular capsule exposed. (Plate XXI.) This step of the operation is of the utmost importance as it affords the proper plane of cleavage, otherwise the surgeon will err in the wrong place and the operation will become very difficult. Two index fingers are introduced between the surgical capsule and the goiter itself and conducted up and down gently around the goiter so as to loosen the tumor from its connection with the surgical capsule. (Plate XXII.) In so doing one often finds the middle or accessory veins of Kocher, which in large goiters are sometimes markedly developed. They are doubly clamped and cut.

7. Now comes one of the most important steps of the operation, a method first introduced by Kocher and called *dislocation of the goiter*. One or two fingers passed posteriorly between the gland and the surgical capsule lift the gland forward, the isthmus forming, so to speak, a hinge upon which the lobe is swung. The surgical capsule is detached and retracted posteriorly as far as the "danger zone" (Plate XI, Fig. 2), but no farther, so as to avoid coming in contact with the parathyroids and inferior laryngeal nerve. Dislocation, too, should not be pushed too far, so as to avoid the danger zone. Occasionally there may be some hemorrhage from small vessels torn when the gland is luxated. This hemorrhage can usually be easily controlled.

This ligation is best obtained by carrying through and through the parenchyma a thread carrier loaded with silk. This affords a good hold on the goiter and is of great help in bringing down the upper pole within easy reach. Two, three, or more of these threads may have to be placed before the upper pole is reached. (Plates XXIV, XXV, XXVI.)

In uncomplicated cases, with not too large a goiter, when the surgical capsule has not undergone any secondary inflammation and has not become adherent to the glandular capsule, dislocation of the goiter is an easy matter, and of most impressive effect, especially when unsuspected intrathoracic goiters are fished out. If, however, peristruinitis has taken place, as in some cases of Basedow's disease, strumitis, and malignancy, the surgical capsule being fused with the glandular capsule propria, it is no longer possible to separate them, the good plane of cleavage cannot be entered into. Under such circumstances the operation becomes difficult and bloody. It is in such attempts to luxate the goiter that alarming hemorrhages are observed, sometimes so intense that one fears to have injured the internal jugular or subclavian veins. Under such conditions luxation must often be given up, and resection of the goiter, after having ligated the upper pole and possibly the inferior thyroid artery, must be undertaken *in situ*. The operation is more difficult but is technically feasible, as shown by surgeons who never luxate, but dissect the entire gland free from its attachments by sharp dissection with scalpel and dissecting forceps, laying bare the posterior capsule. (Plate XII, Fig. 1.) We have seen, however, that such technic is not to be recommended.

8. The upper pole is freed from all surrounding structures, and the left index finger is placed between the upper pole and the carotid sheath so as to prevent injury to the structures contained. A curved, blunt thread-carrier, loaded with silk, is swung around the upper pole and ligation of the thyroid vessels is made. (Plate XXVII.) Usually it is easier to ligate the upper pole so as to bite off a little of the thyroid tissue. A safety hemostat is placed outside of the ligature. This is done for



PLATE XXII

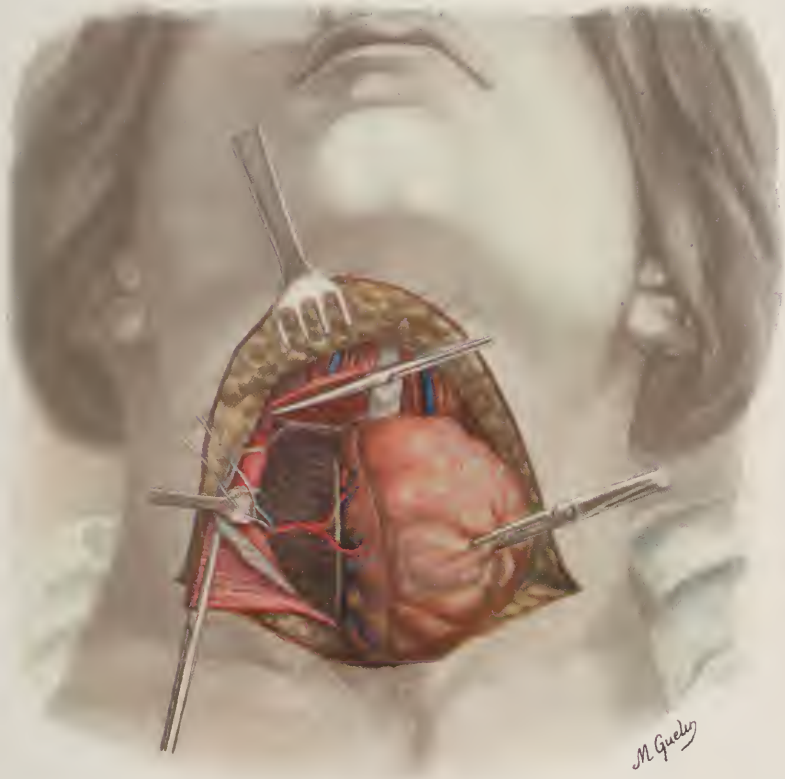


Thyroidectomy.

The surgical space is then fully enlarged and the surgical capsule is retracted as far back as necessary, keeping in mind that it should not be retracted too far into the danger zone. The glandular capsule is thus fully exposed.



PLATE XXIII



Thyroidectomy.

Showing how far back it is safe to retract the surgical capsule and where the ligation of the inferior thyroid artery should be performed in order to avoid injury of the inferior laryngeal nerve and the parathyroids.





security's sake so as to make doubly sure that no postoperative hemorrhage will take place. Another hemostat is placed outside of the first, then the upper pole is severed with scissors between the two hemostats just mentioned. It is tied again, this time with catgut. The upper pole may be so thick as to necessitate several hemostats before it can be entirely severed from the body of the gland.

9. If one is a partisan of the systematic ligation of the inferior thyroid artery, or if it has become evident from the nature of the goiter

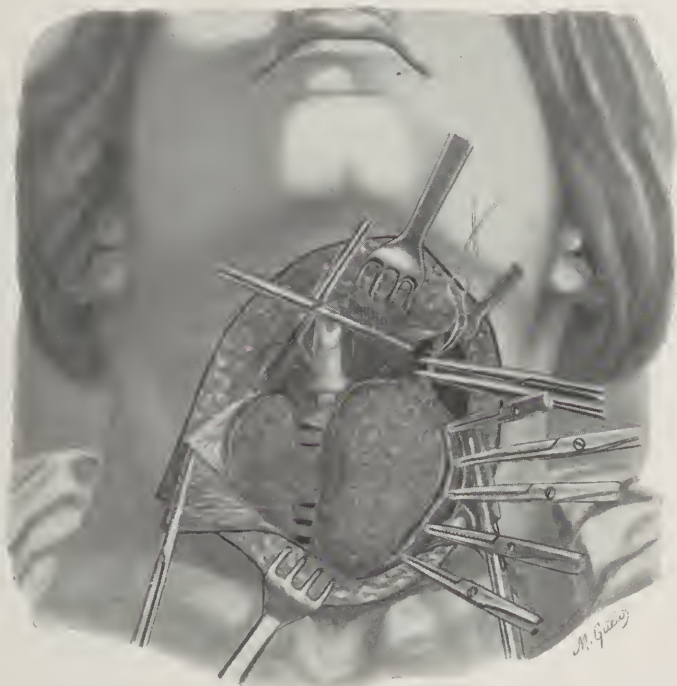


FIG. 88.—The left lobe is then resected in a similar way as was the right. The picture, for clearness' sake, shows that the right lobe and isthmus have been separated from the body of the left lobe. In the ordinary technic of bilateral resection it is more elegant to leave the various portions of the thyroid in close relation one with another so as to remove them *en bloc*.

that this ligation must be undertaken, it is now the proper time to perform it. On account of the reasons given in the chapter concerning ligations, it must be done far from the danger zone at the point of election, namely, just inwardly of the carotid sheath. (Plate XXIII.)

10. When once the upper pole is tied, one goes straight to the lower pole where the bloodvessels are clamped. This is facilitated by traction upon the goiter with the thread that has been placed through the parenchyma or by traction upon the goiter forceps which have replaced the

threads. At the lower pole one or two hemostats will take care of the little bundle of ima veins which are always present. No special effort is made to discover if a thyroid ima artery is present or not. The whole bundle of ima vessels is clamped *en bloc*.

11. Starting at the lower part of the lobe and all along the external edge of the gland (Plate XXVII), and progressing gradually inwardly toward the middle line, hemostats are placed first upon the glandular capsule, and when this has been cut, upon the parenchyma itself and so on until the entire portion which was intended to be removed has been resected and until one has reached the isthmus.

This mode of removing the gland is known as the *transfrontal resection*. If one wishes to resort to the *cuneiform resection*, it is done in the way and manner described in Plates XIII and XIV. Whatever method is employed, great care should be taken to leave a thick enough portion of glandular tissue over the danger zone so as to protect the parathyroids, inferior laryngeal nerve (Plate XXIX, Fig. 92.) and to safeguard the patient against hypothyroidism.

12. What shall we do with the isthmus? Unless one has to be very economical with thyroid tissue, the isthmus had better be resected. If resection is undertaken, it is better to start the resection at its lower border, at the junction of the isthmus and the trachea. A pair of closed blunt scissors is introduced between the isthmus and trachea, then opened. (Plate XXX.) When once the proper plane of cleavage between the isthmus and the trachea is found the operation goes on easily. Resection may be either frontal or cuneiform. If one wishes to leave a thin strip of glandular tissue in front of the windpipe, he may do so (Figs. 91-92.) ordinarily, however, it is better to lay the trachea bare.

13. If the operation must be bilateral the technic just described for the removal of one lobe is applied in the same way for the other lobe which is to be removed. If the prelaryngeal muscles have not been severed before, they are then retracted, the goiter is luxated, its superior pole and if necessary the inferior thyroid artery are ligated and resection is undertaken in the way just described (Fig. 88). Resection may take place either from the middle line toward the outside as shown in the figure or *vice versa*. I prefer to resect from outside inwardly. Here, too, enough gland should be left in order to protect the parathyroids, the inferior laryngeal nerve, and to form with the portion left on the other side a regular contour of the neck.

14. The pyramidal process is dissected out from below upward to its terminal point. One should always be sure to remove all of it, otherwise compensatory hypertrophy will take place later in it and give rise to an unpleasant deformity of the neck.

15. As a general principle the thyroid gland should not be removed iecemeal. It is far more elegant to resect it *en bloc*, its two lobes,

PLATE XXIV

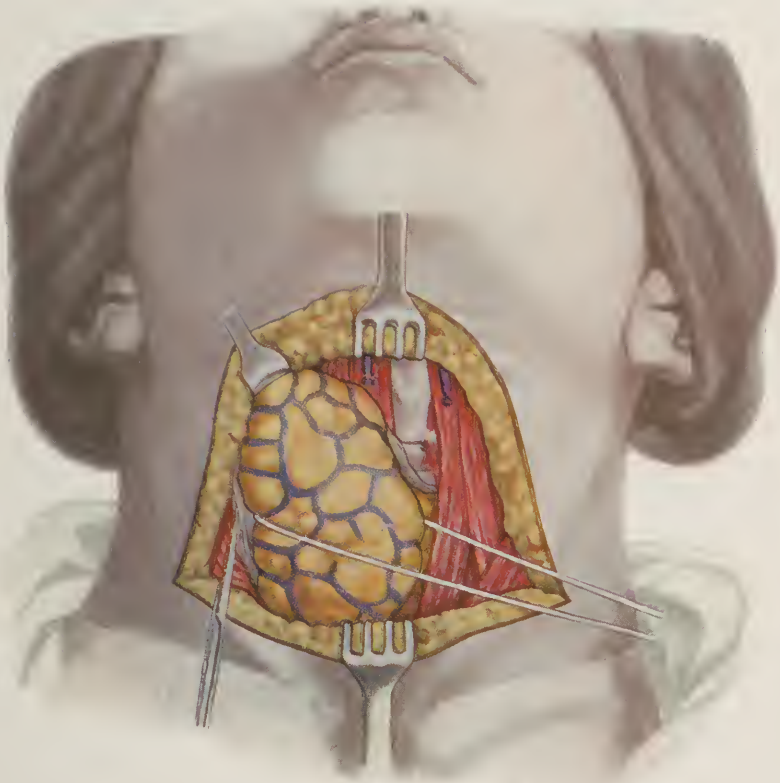


After the surgical capsule has been well reclined, the goiter is transfixed with a hook threaded with silk. This allows an easy traction to be made on the goiter.





PLATE XXV



Dislocation of the goiter.



isthmus and pyramidal process being still in connection one with the other so as to form a whole.

16. Fresh, sterilized towels are put all over the soiled ones and careful ligatures of whatever has been clamped are undertaken. I admit that it is sometimes tedious work, but it is the only way to prevent secondary oozing. And even then one cannot always guard against that. Before removing the safety hemostat on the superior thyroid



FIG. 89.—The prethyroid muscles are then sewed together by a continuous running suture, which is preferable to the interrupted one shown in the picture.

artery, another safety ligation should be performed so as to avoid a secondary arterial hemorrhage. Sometimes, indeed, the first polar ligation does not hold, or the knot is apt to slip, hence the necessity for another safety ligation.

17. A careful exploration of the upper mediastinum is made for thymus hyperplasia. If such hyperplasia is found to be present, thymectomy is performed. Description of the technic for this operation will be found in the chapter on Thymectomy.

18. When hemostasis has been complete, and only then, 15 minims of a 1:1000 adrenalin solution are given subcutaneously, in order to obtain vasoconstriction of the bloodvessels and thus to diminish the

chances of postoperative oozing. When there is a parenchymatous oozing difficult to control, packing of the wound for a minute or two with very hot compresses proves to be very effective.

19. The prethyroid muscles are then sewed up at their upper end and in the middle line by continuous suture so as to restore the normal anatomy of the neck (Fig. 89). The necessity of sewing them is not an absolute one; probably more often than is expected the sutures do not hold; yet this seems to have no ill effect upon the cosmetic aspect of the neck. Some surgeons, Riedel for instance, do not sew them up at all. This procedure, however, is not anatomical and should not be recommended.

20. In the majority of cases drainage is not necessary. If, however, a drain is to be inserted, it must be done before entirely closing up the muscular belt in order to put the end of the drain in its proper position so as to avoid pressure on the windpipe or scratching of the raw surface



FIG. 90.—Intradermic suture is then performed. The picture shows where the glass drain, when used, should be inserted.

of the thyroid, which might cause hemorrhage. Following Kocher's example, I use exclusively a glass drain in thyroid surgery. There is no need of a special opening for this drain. Drainage through the incision as shown by Fig. 90 gives the best results.

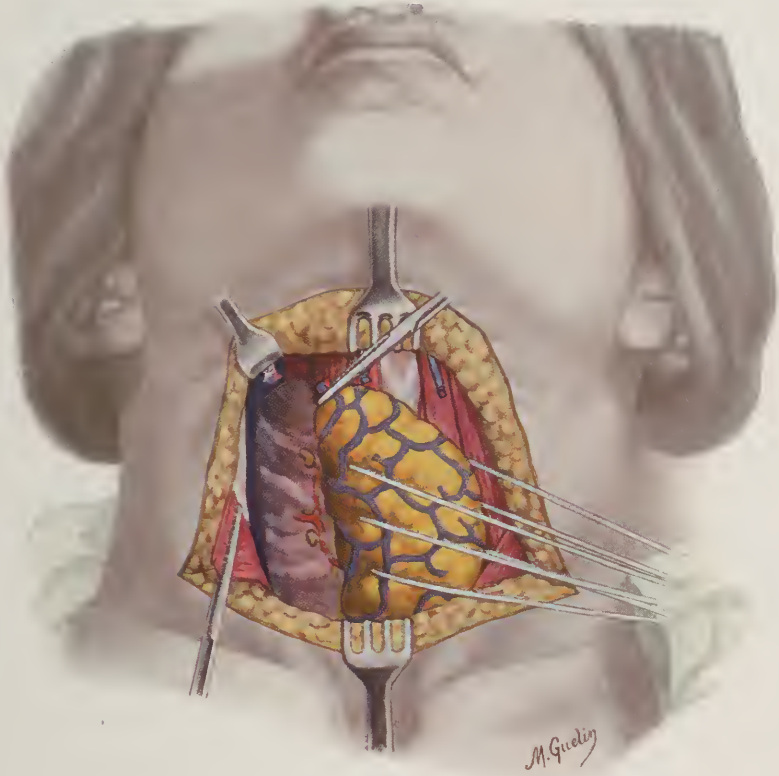
*Transverse drainage*, as suggested by Bartlett, gives, too, very satisfactory results. The drain emerges at each corner of the wound and lies between the skin-flap and the muscles, or below the prethyroid muscles, or in both places.

21. The platysma myoides muscle is sewed up by itself with a continuous suture. (Plate XXV.) This is done in order to avoid later on the spreading of the scar due to traction of this muscle upon the edges of the wound.

22. Intradermic suture of the skin is then made (Fig. 90).



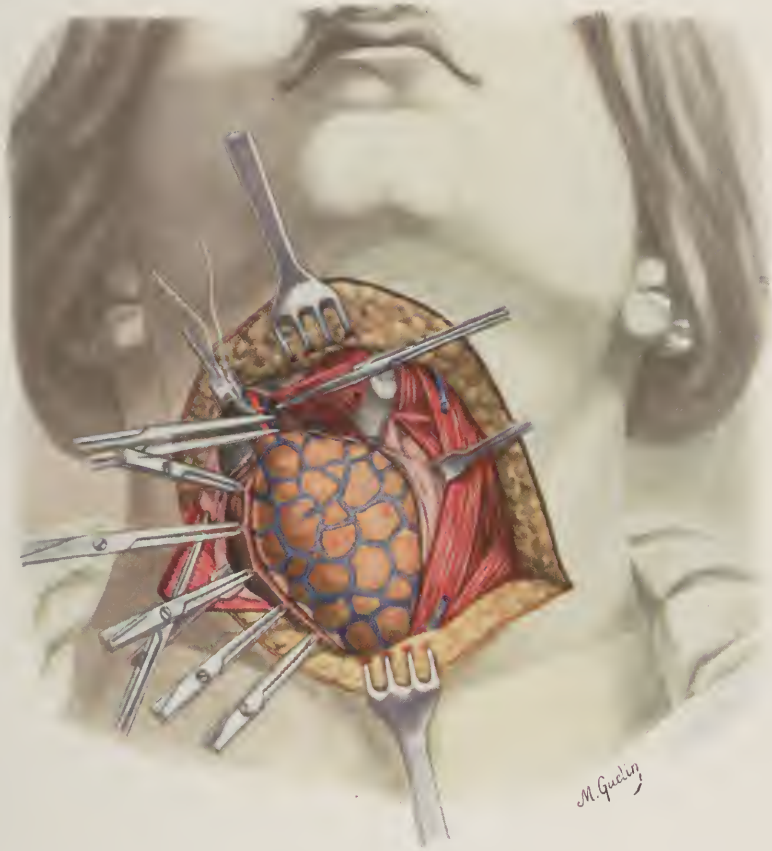
PLATE XXVI



By inserting two or more similar silk threads through the parenchyma of the goiter and exerting a downward traction, the upper pole is brought into view. It is then tied and cut.



PLATE XXVII



Thyroidectomy.

Ligation of the upper pole is performed, the goiter is dislocated forward and a transglandular resection is made, starting at the lower pole and going upward along the lateral surface of the goiter until the upper pole is reached.





## OPERATION FOR INTRATHORACIC GOITER.

The operation is difficult and requires much technical experience and thorough anatomical knowledge. A low-collar incision is made in the same way and position as for any operation for goiter. The pre-thyroid muscles are divided in the middle line and at both upper ends.

The most important thing in such an operation is to free the cervical portion of the goiter as completely as possible from every connection with the other organs before undertaking the removal of the goiter; consequently the upper pole must be ligated and cut. The lobe to be removed must be resected as far down as possible, the hemostasis must be complete before attempting to remove the intrathoracic portion of the goiter. When once freed from its connection with the other organs this cervical portion is used as a tractor to pull the intrathoracic portion of the goiter upward. It is oftentimes the only hold which we can have on the intrathoracic portion, consequently, every precaution should be taken to preserve such connection. At this stage of the operation, it is often possible to pass a finger or two around the lower pole of the goiter and to dislocate it upward. If it is not possible to do so, then the goiter is pulled upward by its cervical portion, slowly, gradually, carefully, each vessel coming in contact with the capsule of the goiter, being clamped securely. It is safer to ligate at once the vessels in contact with the lower portion of the goiter, because otherwise, if ligation is done only after removal of the goiter, the raw surface in which the goiter was imbedded is aspirated again into the thoracic cavity, then ligation becomes extremely difficult and may give rise to tremendous hemorrhages. When the intrathoracic goiter has no cervical portion, and when there is no hold to pull, the goiter is seized with the special forceps devised by Kocher.

In intrathoracic goiter surgery, the critical time of the operation is the moment when the goiter is fished out of the thorax and passes the so-called "critical space," namely, the superior opening of the thorax. At that time alarming hemorrhages and choking of the patient may occur. Blood sometimes gushes up in streams as from a deep well and may be due to injury to one of the large veins, the internal jugular, the subclavian, or the innominate. Suffocation is due to the fact that the goiter in passing the superior opening of the thorax flattens the wind-pipe. It is often necessary to replace the goiter in the thorax in order to allow the patient to breathe again. This may have to be done several times during the surgical procedure until the goiter has passed the "critical point," namely, the superior opening of the thorax.

The intrathoracic goiter may be so large that it is impossible to pull it through the superior opening of the thorax. If we have to deal with a cyst the difficulty is easily turned. The cyst is punctured and its

contents aspirated. If the tumor is solid then the method known as "evidement" or "morcellement" used in bone surgery or in fibroid of the uterus can be successfully applied here, too. One finger goes firmly through the tumor and shells it out piecemeal. Then when the goiter *in toto* has been so reduced in size as to pass the superior opening of the thorax, it is pulled out of the thoracic cavity.

In intrathoracic goiter, drainage is indicated because there is a large, dead space located at the lower end of the wound, consequently this cavity is bound to fill up with blood. No packing should be left in unless hemorrhage should be abundant and cannot be controlled.

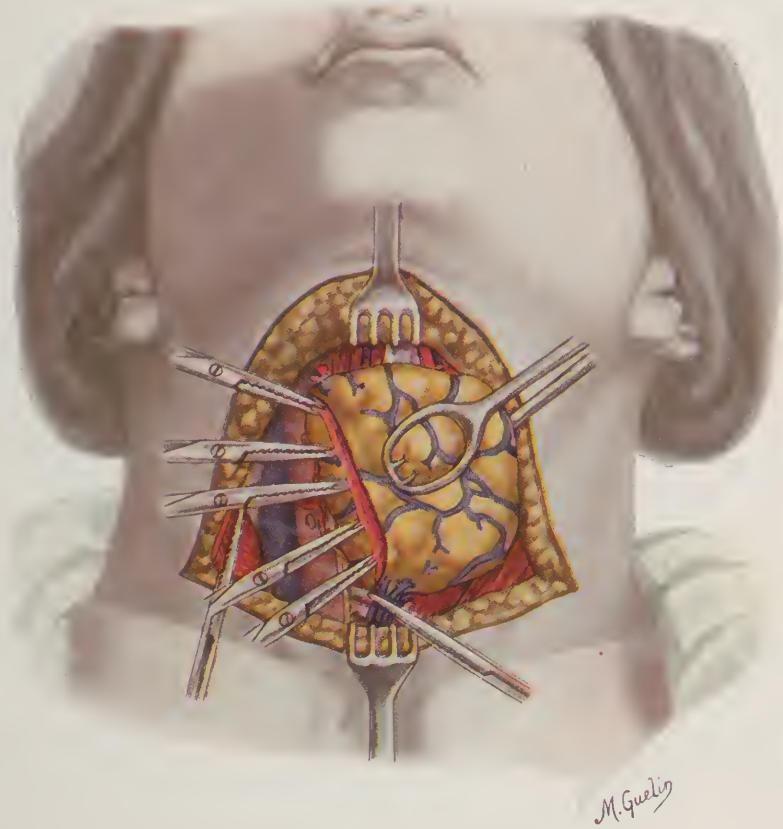
Intrathoracic goiter surgery is one of the most thrilling there is. If one is seeking surgical emotion, it is surely in this field that he will find what he is looking for.

#### TECHNIC OF OPERATIONS FOR MALIGNANT GOITERS.

For this class of tumors it is impossible to set down hard-and-fast rules. The technic will vary with the development of the malignant tumor. In the great majority of cases a malignant goiter develops from a preëxisting simple goiter. For a certain period of time the growth remains intraglandular, leaving the capsule entirely free. If one is fortunate enough to meet with such cases the technic will not be more difficult than in any ordinary goiter. The only thing to do is to perform a total unilateral or bilateral excision as the case may be. Postoperative hypothyroidism should be a secondary consideration, since we know that cachexia strumipriva occurs only once out of two or three cases of complete thyroidectomy. At any rate we have not the choice. If symptoms of hypothyroidism develop, thyroid opotherapy will remedy such complications. Tetany may develop, too, but can be successfully met with our modern methods of treatment.

Unfortunately, in the greatest number of instances the surgeon sees such cases only when the growth has already invaded the capsule and the neighboring tissues, as the trachea, esophagus, large bloodvessels, and the nerves. In such conditions complete removal of the tumor is impossible: operation, if at all performed, can be only palliative.

PLATE XXVIII

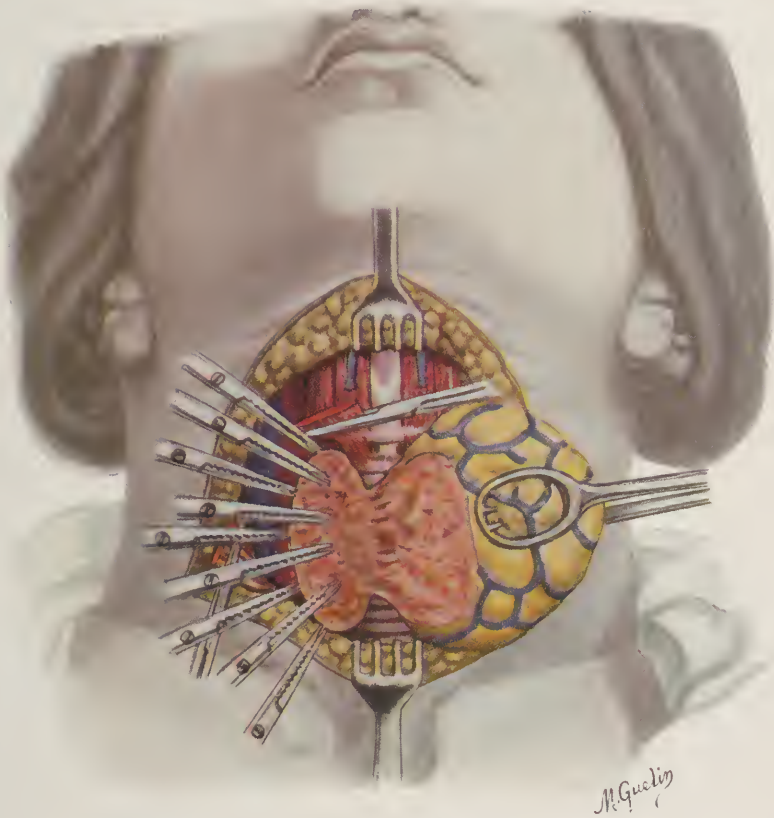


When once the upper pole has been tied and cut, the silk threads used for traction are removed, and replaced by goiter-grasping forceps. The lower pole is exposed, clamped and cut. Hemostats are placed from downward to upward, far enough from the danger zone to avoid injury to the inferior laryngeal nerves and parathyroids. After placing each hemostat the gland is cut.





PLATE XXIX



Resection goes on through the entire body of the lobe until the portion of the gland adjacent to the windpipe is reached. It is better to place the hemostats first and to cut afterward.



## CHAPTER XLII.

### OPERATIVE ACCIDENTS.

**Lesions of the Nerves.—Loss of Voice.**—Injuries to the inferior laryngeal nerves were extremely frequent when total thyroidectomies were performed and when the technic of goiter operation had not reached its present state of development. Billroth, for instance, in 71 extirpations of goiter had 23 partial or complete paralyses of the larynx. In 1885, Jankowsky in 100 goiter operations observed paralysis of the vocal cords 14 times. Today these accidents are rare and with good technic should not occur.

Many authors have reported cases of vocal disturbances existing before the operation which disappeared very soon after goiter had been removed. In such conditions the disturbances are caused by a simple irritation of the recurrent nerve on account of pressure. As soon as the goiter has been removed, pressure ceases, hence *restitutio ad integrum* of the nervous function. In other conditions the vocal disturbances are caused by a congestive condition of the larynx, caused by pressure from the goiter on the laryngotracheal tube. There, again, as soon as the goiter is removed, compression disturbances and congestion cease, while the vocal cords return to their normal condition, and consequently to their normal function.

Injury to the inferior laryngeal nerve is most liable to occur:

1. When the inferior thyroid artery is ligated; hence the indication to perform that step of the operation far from the thyroid, namely, on the inner border of the carotid sheath.

2. When resecting the gland; hence the indication to leave a thick layer of glandular tissue in connection with the posterior capsule.

3. When clamping blindly a bleeding vessel in a pool of blood, the bleeding vessels must be located first and then only clamped.

4. When delivering the goiter too forcibly and using too freely dry sponge dissection in the danger zone.

5. When clamping the lower poles too near the line of passage of the recurrent nerves, it is well to follow Judd's suggestion, namely, to include a bit of thyroid tissue in the clamping hemostat.

If these requirements are observed there should be no direct injury to the inferior laryngeal nerves. It must be said, however, that a temporary, and even a permanent, paralysis of the vocal cords has been

observed even when no direct injury whatsoever to the inferior laryngeal nerve was done. Wölfler found 12 of such cases. Paralysis in such cases is due, either to formation of connective tissue around the inferior laryngeal nerve, on account of ligatures placed too closely to the nerve, or is associated with a previous paretic condition of the vocal cords caused by the goiter itself. Hence the indication never to forget to make a laryngoscopic examination of patients affected with goiter, as a unilateral abductor paralysis or lagging of one cord, is not uncommonly found in goiters of long duration. Such a systematic examination will not only reveal unsuspected paretic or paralytic conditions of the cords, but will also be a protection to the surgeon, since it enables him to warn the patient that a hoarseness or even temporary loss of voice may follow the operation.

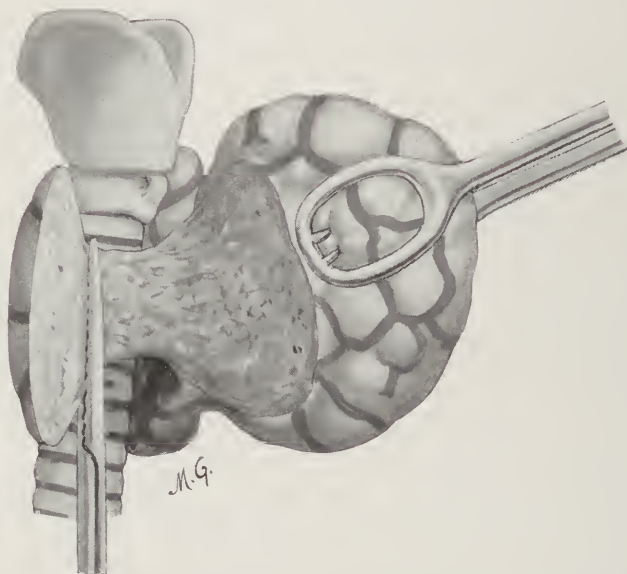


FIG. 91.—The gland tissue connecting the isthmus and lobe is then resected, thus entirely exposing the windpipe.

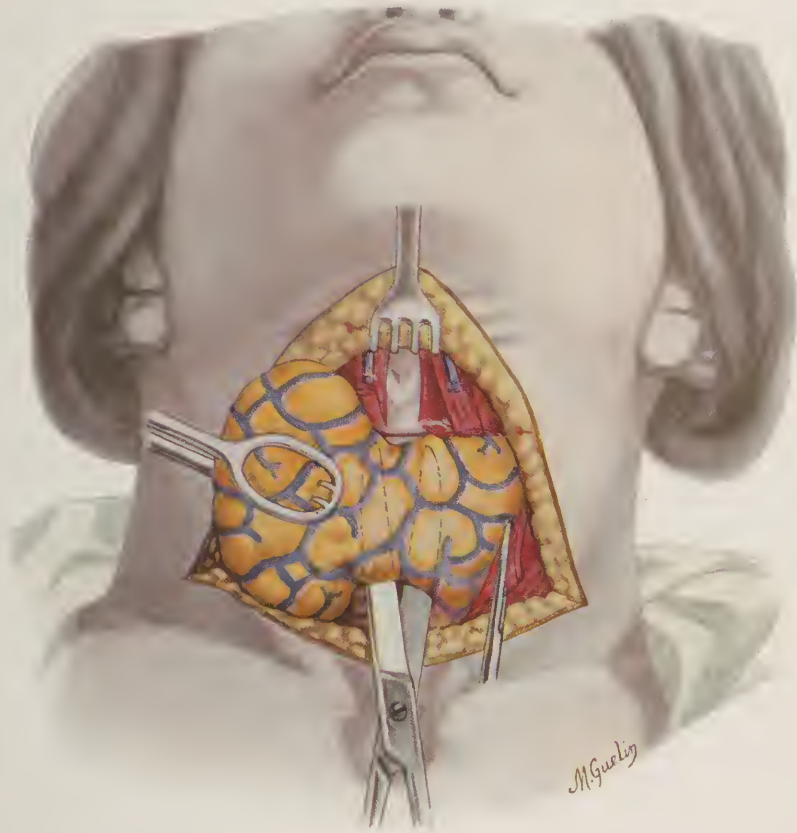
Injury to one of the inferior laryngeal nerves is of good prognosis. If the nerve has been accidentally resected or pinched in a ligature, its continuity is never reestablished, although the patient will in time recover his voice on account of the compensatory swinging over of the other cord. Phonation will in time become so improved that the patient is unaware of any change. The loss of voice seldom lasts more than two to six months. A certain huskiness may, however, remain a while longer.

Bilateral injury of the inferior laryngeal nerves is not common. In 1890, Wölfler reported 6 of such cases. Four times death occurred from pneumonia.

I remember seeing one case of bilateral injury to the inferior laryn-



PLATE XXX



The partially resected lobe is reclined outward as shown above and a pair of blunt closed scissors is inserted between the windpipe and isthmus and spread open, thus separating the isthmus from the trachea.



PLATE XXXI



Thyroidectomy.

The platysma myoides muscle is sewed up by itself by a continuous running suture.





geal nerve after thyroidectomy, in Roux's clinic, Lausanne, Switzerland. The diagnosis was made by the laryngologist. The patient was a young girl who soon after the operation showed alarming symptoms of suffocation and total loss of voice. However, the patient did not die. The remote results in this case were good.

The loss of voice can be total or partial. In the first case the patient can only whisper; in the second case the voice is hoarse.

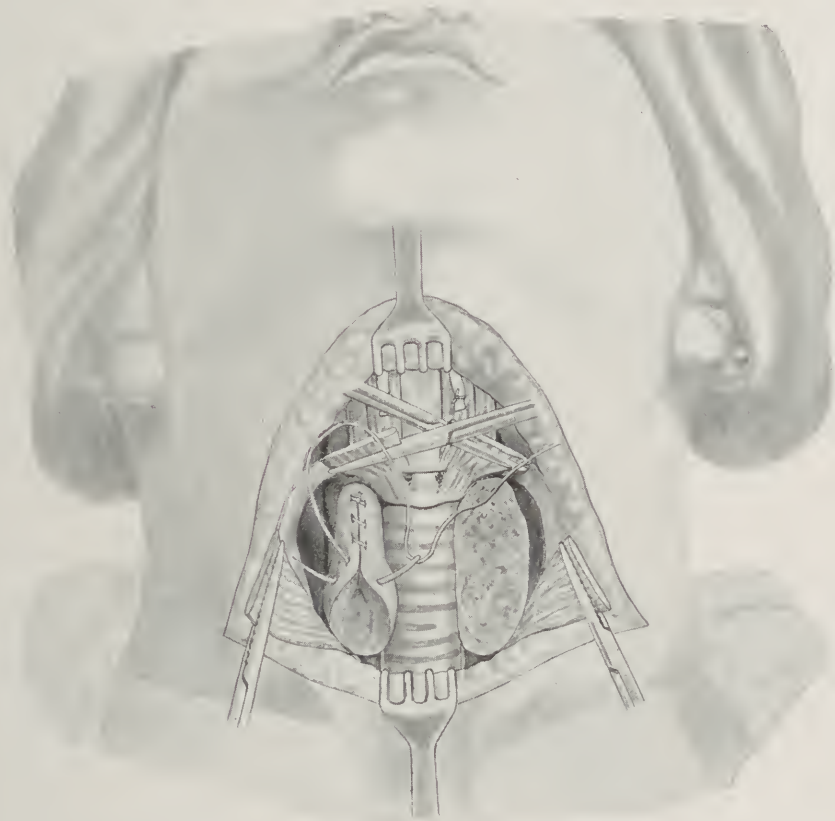


FIG. 92.—The remaining stumps of the dissected gland are either treated as shown above, on the right side by continuous suture, or the surface is left bare. Note the wind-pipe absolutely bare of thyroid tissue in front.

Mann and New have shown that section or ligation of the recurrent nerves with any kind of suture material produces a permanent loss of voice, while pinching of these nerves with a hemostat carries with it a temporary loss of voice only. They also found that forcible stretching of the inferior laryngeal nerve had no effect upon disturbing the nerve function.

These results are corroborated by clinical observations which have revealed that injury.

Leischner collected 67 cases of postoperative troubles of varying degree due to the injuries mentioned. In 4 cases there was paralysis of both cords; 6 cases of unilateral paralysis; 35 cases of unilateral paresis; 19 cases of slight unilateral paresis; and 3 cases of slight bilateral paresis. The final results in these cases, as to the return of the vocal function, were as follows: Of the 4 cases of bilateral paralysis, 2 patients regained normal voice and 2 remained very hoarse. Of the 6 cases of unilateral paralysis, 3 patients regained their voices, 2 remained hoarse and 1 was hoarse occasionally. Of the 19 cases of unilateral paresis of slight degree, 17 regained their voices and 2 remained hoarse. Of the 3 cases of bilateral paresis, the voices became normal. Of the 35 cases of unilateral paresis, 22 regained their voices, 2 remained hoarse, and 4 were hoarse occasionally.

Injuries of the superior laryngeal nerve are rare. Injuries of the phrenic and sympathetic nerves may occur only in malignant goiters. Injury of the hypoglossus may accidentally occur in large goiters extending high up into the submaxillary region. Injury to the vagus nerve occurs frequently during removal of malignant goiters. Not so uncommonly the nerve must be cut away with the tumor. Usually the division or resection of the vagus is harmless. Its irritation, however, through stretching or pinching with a hemostat, is far more serious, since it may lead to diminished cardiac action, lowered blood-pressure, dyspnea, and even collapse and death.

Trauma to the *external muscles of the larynx* never causes permanent loss of voice. The disturbance is only temporary. It is mostly due to the disturbed intermuscular action of these muscles. The concomitant laryngitis which follows such injuries is partially responsible, too, for the trouble.

Injuries of the trachea *per se* do not cause loss of voice. At the most they produce an unpleasant tracheitis which may render the voice more or less husky.

**Tuberculosis and Syphilis** of the larynx are not very common and when present will be diagnosed before performing thyroidectomy. A luetic mediastinitis in its incipiency might be overlooked and its symptoms of shortness of breath and huskiness of voice might be erroneously referred to a goiter. If, however, a routine *x-ray* examination of the chest is made, suspicion will be already aroused. Furthermore, if laryngoscopic examination is made and if a *bilateral abductor paralysis* is found, in New's judgment the diagnosis of syphilis will have to be made.

**Hysteria.**—Guthrie is quite right in saying that there is a strong hysterical element in certain patients losing their voice after thyroidectomy. Some of these patients come for operation with the fear that they will lose their voice afterward. If a close watch is kept on them while they are coming out of the anesthetic, it will be found that their voice

is still normal. Only when they have become conscious do they lose their voice. This fact is already strongly suspicious of hysteria. Furthermore, if laryngoscopic examination is made and a *bilateral abductor paralysis* is found, in New's judgment, this will be enough to make the diagnosis of hysteria. This hysterical aphonia usually does not last very long; at the most, a few weeks. There are, however, some rebellious cases which may cause considerable worry to the surgeon, patient, family and community, especially if untimely remarks have been dropped by a thoughtless or unfriendly laryngologist who may have examined the patient during the stage of aphonia.

**Delayed Loss of Voice.**—Sometimes five to ten days after thyroidectomy loss of voice occurs. Here, no direct injury to the recurrent nerves, to the larynx, to the trachea, has been made at the time of operation. There is no syphilis, no tuberculosis, no hysteria. In such cases the loss of voice is due to the formation of connective tissue from a ligature placed in the immediate vicinity of the recurrent nerve. This is more likely to occur if silk has been used. In these cases, too, the disturbance is temporary.

The causes of temporary loss of voice after thyroidectomy may be put under four headings:

1. Injury to the inferior laryngeal nerve.
2. Injury to the external muscles of the larynx.
3. Syphilis and tuberculosis.
4. Hysteria.

**Suffocation and Collapse of the Trachea.**—One of the most dramatic accidents which may occur during goiter operation is *suffocation*. It is found mostly in connection with partially or totally intrathoracic goiters. It is due to occlusion of the windpipe, either because the trachea is compressed by the tumor when passing the superior opening of the thorax, or because the displacement and compression of the windpipe are exaggerated during the operative maneuvers. And strange as it may seem, suffocation may occur even after the goiter has been entirely removed. At first this seems paradoxical. We have seen, however, that in long-standing goiters pressure causes atrophy of the tracheal walls; they consequently become soft and pliable. While the goiter is present it acts as a splint and supports the weakened portion of the trachea. But suppose we remove the goiter. No longer reinforced by the goiter and having lost their normal elasticity the walls of the trachea are sucked in with each inspiration. The more violent the efforts at each inspiration, the more complete will be the occlusion, because the atrophied walls are drawn into the tracheal lumen like a valve, and as mechanical obstruction of the windpipe is always accompanied by catarrh and edema of the laryngeal and tracheal mucous membrane, the lumen of the trachea available for respiration consequently becomes utterly insufficient. If

the operation is performed under local anesthesia, the patient will soon protest in such a way that the surgeon is bound to know that something is radically wrong. Even if general anesthesia is used, and if the accident happens during the operation, the surgeon will soon locate the trouble. But if the accident happens after the operation is over, if the surgeon has not noticed during operation the condition of the trachea, and if he is not aware that such an accident is possible, he will think that he is confronted with a case of cardiac collapse, of thymic hyperplasia, or will incriminate the anesthetic. In the meantime the life of the patient will be fast slipping away.

If suffocation takes place during the passage of the goiter through the superior opening of the thorax during the act of fishing it out of the mediastinal space, and if luxation cannot take place very quickly, as already stated, it is better to push the goiter back again into its former place in order to relieve pressure. This may have to be done several times until the goiter has been sufficiently loosened from the surrounding structures and removed. In some other instances luxation must, on the contrary, be completed very quickly, as suffocation will cease only when this luxation is complete.

If suffocation is due to an aspirative collapse of the tracheal walls on account of their atrophy, the case is a little more difficult to handle. The ordinary tubes for larynx intubation are of no value because the obstruction lies lower than these tubes can reach. Catheterism of the trachea with catheters used for intratracheal insufflation are the only ones which can be useful. They may be left *in situ* until the walls of the trachea have become self-supporting.

The best plan, however, which has proved successful with other surgeons and myself is to pass at the time of the operation one or two threads through the collapsing walls and to suture them to the muscular belt, with just enough tension to maintain the collapsing walls far apart, but not so as to tear the suture through. The head should then be immobilized so as to set the cervical muscles at rest. The threads will hold just long enough to allow the trachea to become adherent in its new position to the neighboring tissues, and consequently to prevent any further collapse.

As a means of last resort there remains tracheotomy.

It is really impossible to set down hard-and-set rules for each case. The surgeon himself must decide at the time what is really best to do in each given condition. In that critical moment the decision, experience and skill of the surgeon will be the best assets to guard the patient against death.

**Injury to the Trachea, Esophagus and Pleura.**—In non-malignant goiters, accidental injury of the trachea and esophagus should practically never occur. If it does, it must be charged to an error in technic.



Fortunately, injury of the trachea is practically harmless. If by chance, perforation does take place, whistling through the wound informs the surgeon of what has happened. One should not become unduly excited. Blood should be prevented from entering the tracheal gap and exact stitching with fine iodine catgut will put an end to the accident. Usually no untoward results will occur. For a day or two the patient may raise a small quantity of pink-stained sputum. That is all. Even infection of the wound does not usually take place. It is safer, however, at the time of operation to insert a small drain, in case infection should occur.

In malignant goiters, however, which have grown adherent to the esophagus and trachea, partial resection of the latter organs may have to be deliberately undertaken and a tracheotomy tube inserted. In strumitis such a resection is not warranted.

Injury to the pleural membrane is very rare and occurs in conjunction with removal of intrathoracic goiters.

**Tracheotomy.**—While starting out to operate a goiter a surgeon may be called upon to perform a tracheotomy in patients choking on account of pressure from goiter. In order to be successful the operation must be methodical, and at the same time very rapidly done. It is not always an easy matter to open the trachea while a patient is choking to death, while there is an intense congestion of the entire cervical region, while a large goiter prevents getting at the windpipe quickly, and while the trachea is so displaced and compressed that the anatomical landmarks are completely disturbed. And indeed it is not enough to open the windpipe, but the cannula introduced into the trachea must be long enough to pass the stenosis. This is not always the case, as compression may take place low down in the thorax. Our ordinary cannulas in such cases are not always long enough to reach the stenotic point, hence the necessity of always having longer cannulas provided for emergencies. Such have been devised by several authors especially Verneuil, König, Poncet, etc.

**Air Embolism.**—One of the greatest dangers connected with injury of the venous trunks in goiter operations is *air embolism*. In ordinary conditions the thinness of the walls of the veins, and their natural tendency to collapse, makes air embolism quite unlikely. However, in goiters complicated with strumitis or malignant degeneration, air embolism is very apt to occur, because the veins being adherent cannot collapse. The only time that I have met with such an accident was while removing a malignant goiter. Here the subclavian was adherent to the tumor and was inadvertently injured. Before I succeeded in locating the bleeding vessel and clamping it, enough air had been aspirated into the circulatory system so that death followed two days after without the patient having regained consciousness.

## CHAPTER XLIII.

### SYMPATHECTOMY.

THINKING that Graves's disease was due to a neurosis of the sympathetic system, Jaboulay sought to cure it by performing sympathectomy. The first operation was done by him on February 8, 1896. Jonnesco and Abadie at once adopted the same method of treatment and two years later Jonnesco was able to report 10 cases of sympathectomy with 6 complete cures, 4 improvements, and no deaths. From that time on the operation was performed by a great number of surgeons until 1900, when it gradually fell into disrepute. In 1899, Garré performed a bilateral resection of the sympathetic nerve in a patient who had already undergone thyroidectomy. In this case the exophthalmos was so marked that ulceration of the cornea followed; the resection of the sympathetic remained without any effect. In 1902, Ballacescu and Jonnesco advocated a complete resection of the cervical sympathetic nerve, including the superior, middle and inferior ganglia. In 1908, Kocher had intervened only three times on the cervical sympathetic with 1 success, 1 failure and 1 death. Landström combined in one case thyroidectomy with sympathectomy and obtained a complete cure. In England and America the same disregard for the operation is observed. Curtis performed it 7 times and gave it up as a dangerous operation because he had 3 deaths out of the 7 cases. In 1910, Jonnesco reported 30 operations for Basedow's disease without death. Twice he performed a resection of the superior and middle ganglia and 16 times a cervicothoracic sympathectomy, thus resecting entirely the cervical trunk, including the superior, middle and inferior ganglia. For the time being only two surgeons, Jaboulay and Jonnesco, have remained true to that method of operation.

The most complete statistics we have on that subject are those given by A. Charlier; they refer to the material taken from the clinic of Jaboulay from 1896 to 1910. Jaboulay performed sympathectomy in 31 cases, 23 women and 8 men. In 1 case bilateral *elongation* only of the nerve was performed. In 9 cases the mere division of the nerve, namely, *sympatheticotomy* was performed, twice unilaterally and 7 times bilaterally. In the remaining 21 cases, resection, namely, partial *sympathectomy*, including the resection of the superior ganglion, was performed; 4 times the operation was unilateral and 17 times bilateral; twice only the removal of the middle ganglion was added to it. Four of these cases

had already undergone thyroidectomy without results; 3 of these sympathectomized cases had to undergo a subsequent thyroidectomy on account of failure of the sympathectomy to bring about relief. Out of the 31 cases of Jaboulay's 6 died, thus giving a death-rate of 19.35 per cent. One patient died from thymus hyperplasia. The immediate post-operative course, according to Charlier, was, as a rule, very benign—some fever, some dysphagia, were about all. There was often, however, a complication which seemed to threaten the life of the patient, namely, bronchopneumonia. Four out of the 6 cases of Jaboulay's statistics died on account of pulmonary complications. A very severe hyperthyroidism may follow the operation, as in Duret's experience.

**Pathology.**—The morphological nature of the sympathetic is exceedingly variable; it is consequently difficult to know what is pathological or what is not. In some instances the ganglia, as observed by Herbert, Eulenberg, Guttman, Reith, Moore, especially the superior, are materially increased in size, congested and red. Jaboulay noticed very frequently an increased vascularization of the whole sympathetic. The microscopic examination, made by various authors, of the sympathetic ganglia and cord taken on the whole does not reveal any microscopic changes. On the other hand, L. B. Wilson found definite histological changes in the cells of the cervical sympathetic ganglia in exophthalmic goiter. These histological changes consisted of various stages of degeneration, namely, (1) hyperchromatization, (2) hyperpigmentation, (3) chromatolysis, and (4) atrophy, or (5) granular degeneration of the nerve cells.

So far as could be determined from the small number of observations, the pathological changes in the cervical sympathetic ganglia were parallel to the stage and intensity of the symptoms of hyperthyroidism and to the hyperplastic and regressive changes in the thyroid.

The fact that the exophthalmos retrocedes so quickly has been interpreted as due to the vasoconstriction of the vessels of the orbit. This, however, cannot be the case because we know that section of the sympathetic causes a vasodilatation, as is shown by the congestion of the veins of the conjunctiva and the retina, caused by the vasodilatation of the retrobulbar vessels. Consequently, if the interpretation given were correct, instead of a diminished, we should have an increased exophthalmos.

**Immediate Results of the Operation.**—One of the most constant and most noticeable results is the diminution or disappearance of exophthalmos. This feature is sometimes noticeable on the operating table. It is very likely due to the paralysis of the unstriated musculature of the orbit, especially Landström's muscle. At the same time there is a marked diminution of the widening of the palpebral fissure due to the paralysis of Müller's muscle; the pupils become more contracted.

An exaggerated secretion of the lacrymal glands lasting only a few days is sometimes seen. Jaboulay has observed that a sympathectomy has a peculiar and remarkable influence on certain cases of near-sightedness. It causes a remarkable improvement of vision, the distant vision especially showing such benefit. Jaboulay believes that this is due to the fact that the eyes sink back into the orbital cavity and become smaller as the result of sympathectomy. He bases his contention upon the fact that the more one is near-sighted, the larger and more protruding are the eyes.

Everyone seems to agree that when sympathectomy is successful the subjective symptoms of the patient show a considerable improvement. He becomes more quiet, less impressionable, less agitated, tremor diminishes; tachycardia, however, is little influenced or not at all, and the same is true for the goiter.

In conclusion it may be said that the results obtained from sympathectomy when present are very immediate. The ocular symptoms are the ones most happily influenced by the operation; the others, such as nervousness, tachycardia and goiter, are problematical.

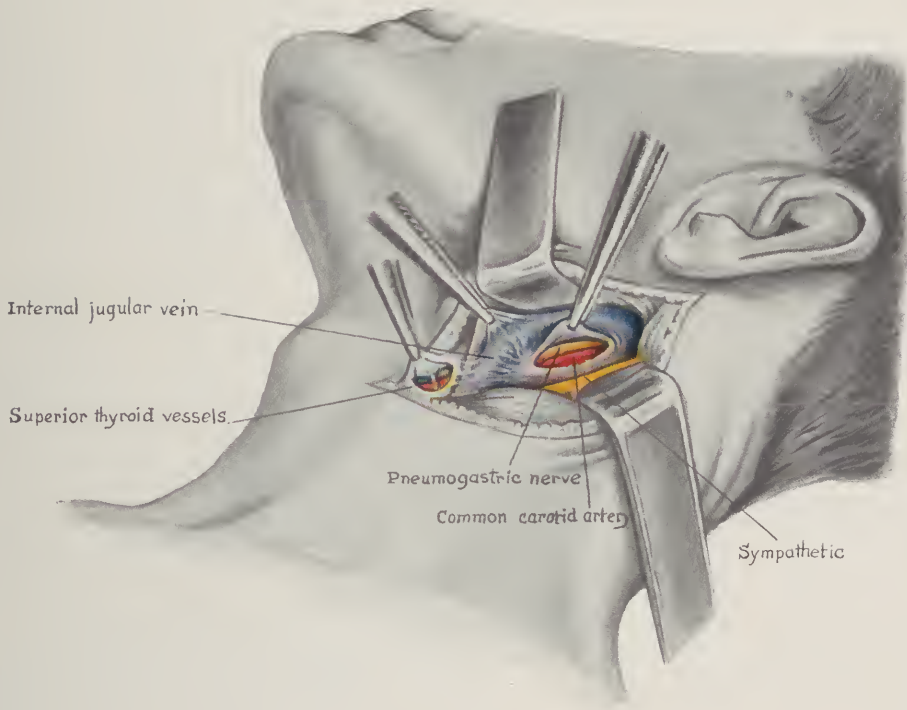
**Remote Results.**—In going over the cases operated by Jaboulay as far back as twelve and fourteen years, A. Charlier was able to find that a number of his patients had been cured completely. He was able to retrace 18 out of the 31 cases operated by Jaboulay from four to fourteen years before. Three of them were completely cured, 9 of them were so ameliorated that the subjective cure was a complete one, the objective cure, however, being incomplete; the 6 remaining cases were doubtful. All these patients experienced considerable benefit to their nervous symptoms; in all exophthalmos had either disappeared or subsided; vision was improved and no trophic disturbances of any sort followed as the result of sympathectomy. The cardiac disturbances and goiter were the symptoms less influenced and the ones in which the improvement showed less.

The impression one gains in going over the literature on this subject is that failures and relapses seem to be quite frequent with this method.

**Choice of Operation.**—The results observed by Jaboulay seem to be more or less the same no matter whether sympathectomy, or sympathetomotomy, or simple elongation of the sympathetic has been done. This is a very important point to note since it follows that extensive operations upon the sympathetic, as for instance complete removal of its cervical portion, including the superior, middle and inferior ganglia, as advocated by Jonnesco, are not only most laborious, most difficult and most prolonged operations, but would also appear to be unnecessary surgical risks. The simple unilateral partial sympathectomy gives sometimes about as good results as the bilateral, yet the maximum of effect is obtained solely by bilateral intervention. The age and sex of



PLATE XXXII



Sympathectomy.



the patients seem to be of no particular importance since the results are the same for young or old, for men or women. The operation upon the sympathetic is especially successful in cases of Basedow's disease where exophthalmos is very marked and where little or no goiter is present. Here, too, the sooner the operation is performed the better the results will be.

**Surgical Technic for Sympathectomy.**—The preparatory treatment of the patient for operation is absolutely the same as for any other thyroid operation. When once it is admitted that an extensive operation involving the entire cervicothoracic trunk of the sympathetic does not give better results than simple partial resection, then this latter operation must be considered as the method of choice.

The location of the incision will depend upon the following conditions: if sympathectomy is going to be the only surgical act, and is not to be combined at the time of the operation or later with thyroidectomy, then the incision should be made parallel to the anterior border of the sternocleidomastoid muscle, the middle of the incision being located at about the level of the upper border of the thyroid cartilage. (Plate XXXII.) If, however, sympathectomy must be combined at the time of the operation either with thyroidectomy or with thymectomy, then the incision had better be the usual transverse or low-collar one, adopted for thyroidectomy. Through the latter incision it is possible not only to remove the thyroid and the thymus, but also to ligate the inferior thyroid artery and to remove the sympathetic which lies, as a rule, just behind the inferior thyroid. If the lateral incision is made, ligation of the upper pole (Plate XXXII) can be made at the same time, as shown by Mayo.

The sternocleidomastoid muscle is reclined laterally. The same is done with the carotid sheath after, however, having located the vagus nerve. The thyroid gland and the thyroid cartilage are reclined inwardly. (Plate XXXII.)

When trying to locate the sympathetic it is well to remember that it lies just behind the carotid sheath on the prevertebral fascia covering the rectus capitis anticus major and the longus colli muscles about one-half centimeter inwardly of the transverse process of the cervical vertebræ. Chassaignac's tubercle, or transverse process of the sixth cervical vertebra, is a good landmark when locating the sympathetic and its middle ganglion in the region of the inferior thyroid. The carotid sheath does not fuse intimately with the cellular atmosphere surrounding the sympathetic, hence the possibility of reclining the carotid sheath laterally, thus leaving the sympathetic exposed and in intimate contact with the prevertebral fascia. It sometimes happens that the sympathetic trunk is not found. In that case it is well to release the carotid sheath from the retractor, as it sometimes happens that in reclin-

ing the vascular sheath the sympathetic follows. This is not frequent, however. The operation is sometimes made more difficult by the presence of hyperplastic lymph nodes more or less adherent to the carotid sheath; in that case the lymph nodes must be removed before access can be had to the sympathetic.

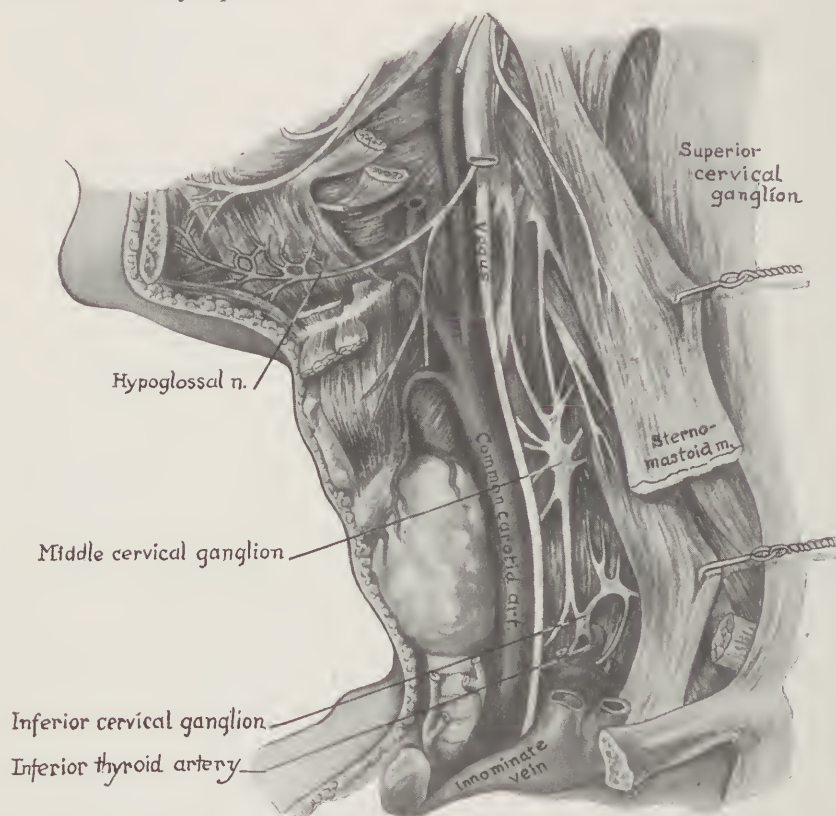


FIG. 93.—Relation of the sympathetic to the surrounding structures. Note the inferior thyroid artery passing between some of the sympathetic fillets. Note, too, the position of the middle cervical ganglion.

As a rule the sympathetic lies directly behind and slightly inward from the vagus nerve (Fig. 93). It must be, as already said, an *absolute rule never to resect* the sympathetic without first having exposed, or at least located, the vagus nerve. When once located the sympathetic is followed as far up and down as possible, and then resected. If the superior and middle ganglion, or one of them only, can be resected at the same time, that should be done.

The removal of the inferior sympathetic ganglion is a delicate operation, inasmuch as it lies in the upper part of the mediastinal space, is of very difficult access, and is surrounded by a number of very important organs.



## CHAPTER XLIV.

### CANTHORRAPHY.

IN some patients despite thyroidectomy and sympathectomy, exophthalmos remains unaffected and becomes a source of trouble and great annoyance to the patient. Such patients are sometimes greatly benefited by a *canthorraphy*. This consists in scalping the edge of both lids from a quarter to a third of an inch at the outer canthus and sewing the denuded marginal portions of the lids.

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## CHAPTER XLV.

### TREATMENT BY INJECTIONS INTO THE THYROID.

BOILING-WATER injections into the thyroid gland for hyperthyroidism have been devised lately by M. F. Porter. This method is based upon the old principle which is at the base of any injection method, namely, to destroy a portion of the parenchyma. We have seen in the chapter devoted to injection methods for simple goiter, that almost any medicament has been used. M. F. Porter uses boiling water, which is less irritative and just as effective as any other means for bringing about degeneration of the parenchyma and the formation of connective tissue instead. It has the same advantages and disadvantages of all the injection methods. It is of simple application and reduces the surgical shock to a minimum, yet Babcock had 1 death from acute hyperthyroidism, and Mayo 2 deaths. The method is not devoid of danger because injection may be made erroneously intravenous. As sloughing and subsequent infection have occasionally been the results of injection methods it is reasonable to assume that this may be the same for the boiling-water method. And so it is difficult to judge how much parenchyma is being destroyed, and the method has, furthermore, the disadvantage of converting the thyroid into a more or less great mass of connective tissue, thus exposing the patient later on to respiratory disturbances on account of compression of the trachea. I can recall a case of parenchymatous goiter which had been treated by medicamentous injections, and in which just such a complication occurred. The patient finally had to be operated upon in order to relieve the pressure symptoms.

The method, however, has its clear indications and may be of great value in preparing for subsequent operations, patients who, for the time being, are too bad surgical risks. In Porter's and Babcock's judgments, this simple operation can very well be compared to ligation so far as its efficacy is concerned. Personally, I have not obtained from the method all that I expected. The response to the treatment has not been as rapid as claimed, and subsequent operations were rendered extremely difficult if time had been allowed to elapse between injection and thyroidectomy. The technic of the operation as given by Porter is as follows.

**Technic.**—"An all-glass syringe of 10 cc to 20 cc capacity is best. The greater the capacity of the syringe the longer the heat of the water is retained. The needle should be long, flexible and rather fine. The syringe is boiled with the water over a gas or alcohol flame by the side of the table or bed on which the patient is lying. After proper cleansing, the areas to be injected are infiltrated with 1 per cent novocain. The filled syringe is removed from the water, which is actually boiling, and the injection quickly made. From 5 to 20 cc are injected, according to the size of the lobe. By partially withdrawing the needle and reinserting it, contiguous areas may be injected through one puncture. Dr. Babcock has made injections in his office, but thinks, as I do, that this is not to be commended. I prefer to have the patients remain quiet for one-half or one hour after the injection is made. The needle punctures are covered with gauze wrung out of alcohol for a couple of hours. Sloughing has never occurred, and the small eschars on the skin produced by the needle are not permanent. The needle should penetrate the skin as nearly as possible at right angles in order to reduce the burning to a minimum. I have been in the habit of handling the syringe with the aid of forceps and gauze, but in the future I shall use Babcock's method, which is better. He wears three pairs of gloves: first, a pair of rubber gloves covered with thick cotton gloves, and over all a pair of rubber gloves. Most patients complain immediately after the injection of a feeling of fulness in the goiter and some pain in the occiput, but the discomfort is really trifling. The injections are to be repeated until the desired effect is attained. If one is using the treatment preparatory to thyroidectomy then it is well to repeat the injections every two or three days, that is, if more than one is necessary; but if one has decided to try to effect a cure by this means, it will be better to wait a week to ten days before repeating the injections, as indicated above. While the improvement is usually marked within the first forty-eight hours, it does not reach the maximum for ten days to two weeks. It is better, especially in the large goiters, to inject two, three or more areas at one séance than to make the injections at intervals. Indeed, I may say that the tendency is, as experience grows, to make large and multiple injections at a single séance, rather than to make

smaller and single injections and to repeat the séances. In some cases with small, ill-defined glands, it is better to make an injection through a small incision in the midline, done under local anesthesia, which will enable the operator to do the work under the guidance of the eye."

**Quinine and Urea Injections.**—Watson, in 1914, recommended the method "only to relieve hyperthyroidism and not to remove the goiter. It is often true that in small toxic and atoxic goiters the inflammatory reaction following the injection is sufficient to cause the disappearance of the tumor; but the process is slow, usually covering several months, and when used for this purpose alone, the results are liable to be disappointing.

"The injection must be employed with discretion. It is suitable for use only in a hospital by men skilled in goiter work. One inexperienced is liable to inject too deeply, or to make the injection within the trachea. The indiscriminate use of quinine and urea, in the hands of one not familiar with the low threshold to stimuli possessed by the average cases of toxic goiter, is liable to produce alarming symptoms which might result disastrously.

"In all cases of hyperthyroidism he has obtained the best results by keeping the patient in bed in a hospital several weeks while giving the injections, the length of time depending on the severity of the symptoms and response to treatment.

"The necessity of minimizing the pain from any injection by the use of local anesthesia cannot be too strongly emphasized.

"To raise the patient's threshold to stimuli, thereby preventing an acute attack of hyperthyroidism which otherwise might follow the slight pain of the first quinine and urea infiltration, all cases of toxic goiter receive at one- to three-day intervals preliminary injections into the most prominent portion of the goiter of a few minims of sterile salt solution followed by injections of sterile water.

"After two to four preliminary injections, the nervous reaction is so diminished that the quinine and urea can be given with only slight discomfort and no increase in symptoms; as soon as there is no hyperthyroidal reaction following the water injections their usefulness is at an end."

Sloan advocates the use of a 50 per cent solution of quinine-urea in cases of very sick patients. Five to 10 cc are injected at one time; the smaller dosage being used in the upper poles and the larger amount in the mass of the gland.

## CHAPTER XLVI.

### PREOPERATIVE TREATMENT OF THE PATIENT.

WHEN the patient is once in the hospital he is to be kept in bed and given rest. Unless there should be vital indication to do otherwise, not only is it an error, but it is *criminal* to operate a goiter patient without a treatment preparatory to operation. This preliminary treatment may last only a few days, or several weeks, just as the case may be.

The room must be well ventilated, the surroundings must be quiet and pleasant, everything must be done to gain the confidence of the patient and his coöperation. He must be induced to "make himself at home." Two or three hours a day he will be allowed to sit up in order to break the monotony of the rest cure. A few congenial visitors may be admitted.

Upon entering the hospital, if the bowels have not been regular, a mild laxative can be given. Subsequently cathartics must be given only if absolutely necessary. The traditional "cleaning of the bowels" the day before operation must be discarded.

Attention should be given to the hygiene of the mouth. Bad teeth should be extracted, pyorrhea treated, tonsils looked after. If the tonsils are in bad condition, tonsillectomy should be performed before thyroidec-tomy is undertaken. In short, every possible source of focal infection must be investigated.

Ten to 15 drops of Digalen Cloetta and 10 to 15 drops of tincture of strophanthus are given daily. In the majority of cases they have a remarkable toni-cardiac effect. If not well tolerated they should be discarded. If bromides, veronal, trional, baldrian are deemed necessary, they must be given.

The last two days before operation the patient, especially if thyro-toxic, is given 150 grams of glucose and 5 to 10 grams of bicarbonate of soda as a preventive of postoperative acidosis. (See chapter on Acidosis.)

The patient must be kept in absolute ignorance of the day and time when the operation is to take place. When he asks, "Doctor, when am I going to be operated upon?" he must be told jokingly, "That's none of your business." He is then told why.

Menstruation is a contraindication to operation, as the nervous system of these patients, especially the thyrotoxic ones, is often very



much disturbed during the menstrual cycle. It is better to wait until this process is over.

No preliminary preparation of the field of the operation is necessary in anyway whatsoever. I found that simple preparation with iodine on the operating table is all that is necessary. The surplus of iodine is washed off with alcohol. When using iodine we must not forget that its disinfecting and penetrating power is far greater when used on *dry skin* than when used on a skin which has just been washed and cleansed. Hence the necessity of performing the preliminary washing with soap, water, alcohol and ether several hours before the operation, when one wants to resort to that method at all.

Forty-five minutes before operation the patient is given  $\frac{3}{4}$  of a grain of pantopon and  $\frac{1}{150}$  grain of scopolamin. (See chapter on Pantopon.)

## CHAPTER XLVII.

### OPERATING ROOM TECHNIC.

ON the table the patient is put in the recumbent position with a hard, triangular pillow under his shoulders so as to overextend the head. The purpose of this is to make the neck as prominent as possible and to put the thorax in a dependent position. It is advisable, if the operating table permits, to elevate the upper part of the trunk slightly and to lower the foot so as to obtain an oblique elevated position. This lessens the venous congestion of the upper part of the body and produces a certain degree of cerebral anemia, thus facilitating anesthesia and reducing the amount of anesthetic used.

The field of operation is painted with iodine, and then washed with absolute alcohol. In thyrotoxic goiters, where one wants to avoid iodine intoxication, alcohol alone is used.

McDonald's solution answers the purpose very well. Here is the author's formula:

Acetone (commercial) . . . . .	40 parts
Denatured alcohol . . . . .	60 "
Pyxol . . . . .	2 "

The operative field is then isolated from surrounding parts with sterilized sheets. The Kocher screen for protecting the field of operation from the mouth is absolutely necessary; no one can be morally certain of his asepsis without it. The hands of the operator, assistant and nurses are washed with hot water and soap for two or three minutes, dried, then immersed in iodine and washed with alcohol. There should be no need to say that, according to modern views on asepsis, no surgeon who is really anxious to be thoroughly aseptic will approach the operating table without having his arms protected up to the wrist with sterilized gowns, his hands fitted with sterilized gloves, and the mouth and head covered with some sterilized device. The same is true for his assistants and nurses.

*Only now after the above preparation shall the anesthesia be started.* Inasmuch as I consider the anesthetic one of the greatest dangers in goiter surgery, I aim to reduce that danger to a minimum. That is the reason why I give the anesthesia at the last moment only, and cease it before the operation is terminated. In the greatest number of cases the

element of excitement and fear during the ten to fifteen minutes during which the surgical preparation is being made prior to the anesthetic is negligible. That is, at least, my experience. If properly explained that it is done for his own benefit and safety, the patient readily consents to being anesthetized in the operating room. Moreover, the presence of the surgeon while the anesthetic is given is always a source of comfort to the patient, as usually he has implicit confidence in him, while he may not have the same amount in the anesthetist whom he does not know. As a general principle general anesthesia must be always light in goiter surgery. Since I adopted that mode of doing, after having tried everything else, my postoperative complications such as hyperthyroidism, acidosis, etc., and my death-rate have been reduced considerably. The more severe the thyrotoxic case is, the stronger, in my judgment, is the indication to reduce the period and amount of anesthesia to a minimum, or even to resort to local anesthesia.

Before the great war broke out I used systematically, as advocated by Crile, the subcutaneous infiltration with novocain. Since, however, novocain remained for a long time unavailable, I have been compelled to do without it. To my great satisfaction, I have not noticed any effect for the worse in the postoperative welfare of my patients. In fact, I do not see any difference. Consequently I have given up the use of novocain infiltration in conjunction with general anesthesia.

The suture material used is silk for ligation of the upper poles and inferior thyroid arteries, and iodine catgut for ligatures and sutures. Silk is used on account of its non-resorbability.

**Thyroidectomy Bandage.**—The usual bandage used after thyroidec-tomy goes around the neck, crosses in front of the chest, passes under the arms, and terminates around the head, thus immobilizing the head and neck and affording a complete protection to the wound against soiling from vomiting, etc. It is the bandage *par excellence* for use in the operating room. When the patient has become totally conscious again, the upper part of the bandage, if found objectionable to the patient, may be cut off by the nurse.

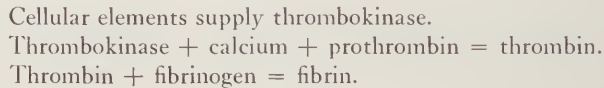
The following day, the whole bandage is removed, the wound cleansed with alcohol and a bismuth-collodion dressing made so as to protect the wound well, but leaving the rest of the neck free. Eight days after, the colloid bandage is removed. Acetic-ether is used to soften the collodion.

**Hemostatic Serum.**—In the last three years, I have given up almost entirely the use of drainage. Only in certain special cases do I resort to the use of drains. I found that careful hemostasis and the use of hemostatic serum (Parke, Davis & Co.) are exceedingly satisfactory. Only rarely do I encounter postoperative hematomas.

Hemostatic serum is a sterile blood derivative originated by Dr.

V. A. Lapenta and composed principally of prothrombin, antithrombin, and thrombokinases in physiologically balanced solution. The preparation of hemostatic serum is based upon the more recent studies of the phenomena of blood coagulation. It has long been recognized that the formation of blood-clot depends upon the evolution of fibrin from the fibrinogen of the blood, through the action of a ferment known as *thrombin*. Thrombin does not exist as such in the blood, but is present as *prothrombin*, and is kept in this antecedent state by the action of a neutralizing substance, designated *antithrombin*.

According to Howell, the normal coagulation of the blood takes place under fairly definite conditions. All the necessary constituents are constantly present in the blood, fluidity being maintained by the action of antithrombin. This substance is neutralized by thrombokinase, which, when the vessels are ruptured, is supplied at once by the cellular elements—leukocytes and platelets—and by tissue fluids. The process of coagulation then takes place in a manner which may be presented by the following equation (Howell):



The fibrin enmeshes the formed elements of the blood, and the clot results.

From this it will be seen that the available quantity of prothrombin in the blood depends upon the proportions of thromboplastic substances and antithrombin, an excess of the first increasing the prothrombin quotient by partial neutralization of the antithrombin, or *vice versa*. This thromboplastic substance, or more properly thrombokinase (Howell) and antithrombin (Howell) are easily demonstrated in the blood serum.

Hemostatic serum contains, as previously stated, prothrombin, anti-antithrombin, and the kinetic material thrombokinase.

The anti-antithrombin is a blood serum derivative, but is not a constituent of the normal blood or tissues. When it enters the blood stream directly, either by intravenous injection, or by any other method of administration, this constituent of hemostatic serum acts specifically on the antithrombin so that the latter no longer prevents the formation of thrombin from the antecedent substance prothrombin.

The thrombokinases present are chiefly concerned in initiating the reaction between prothrombin and calcium ions and the actual production of thrombin.

I use the hemostatic serum locally and hypodermically. The local application consists in packing the wound gently with a piece of gauze saturated in the liquid diluted with about 10 to 15 cm. of hot, sterile



water. For that purpose I aim to liberate one side of the wound by tying all the ligatures on one side of the neck first, so as to allow plenty of time for the coagulation to remain in intimate contact with the tissues. It is very essential that the gauze be brought into contact with the tissues by a certain amount of gentle pressure. When the packing is removed, the wound is absolutely dry, of a grayish-white aspect. If, perchance, a bleeding-point is discovered, it must be tied. Before closing up the wound a certain amount of the diluted hemostatic serum is left in the cavity, not too great an amount, however, since in my experience, when the amount is too great, I have experienced the elimination of the serum through the wound several days after. Now, I am content to leave behind whatever remains in the wound after squeezing out the air of the field of operation just before putting in the final stitch in the prethyroid muscles.

At the same time 2 cc of the same diluted solution is given hypodermically. No local complications have been seen.

In the many hundreds of thyroidectomies that I have performed, I have observed three times symptoms of a mild anaphylaxis, characterized by itching and urticaria, but such conditions were easily controlled by the use of adrenalin and pituitrin. No other anaphylactic symptoms.

I have observed a very severe case of anaphylaxis in the case of my medical associate, Dr. Ramsey, who underwent a tonsillectomy at the hands of a competent specialist and who, on account of postoperative hemorrhage, received intravenous injection of hemostatic serum. An alarming edema of the glottis, of the tongue and of the right kidney occurred twenty-four hours after. This, however, was quickly controlled by adrenalin and pituitrin.

There are other hemostatic agents, which, too, are satisfactory, such as *thromboplastin*, *the coagulen Fonio*, etc. Thromboplastin does not cause anaphylaxis, and this is a great advantage.

## CHAPTER XLVIII.

### POSTOPERATIVE TREATMENT.

As soon as the patient is brought back from the operating room a proctoclysis, 20 to 25 drops a minute, is started. I use the following formula:

Sodium chloride . . . . .	6.0 grams
Calcium chloride . . . . .	1.0 "
Potassium chloride . . . . .	0.3 "
Bicarbonate of soda . . . . .	100.0 "
Glucose . . . . .	150.0 "
Alcohol . . . . .	20.0 "
Aq. dest. . . . .	1000.0 cc

This proctoclysis is kept up for one to two hours and then stopped. A few hours after it may be repeated again. It is an excellent means to combat thirst, and furthermore has the great advantage of increasing the blood-pressure.

Vomiting is present in a small percentage of cases, but is rarely so persistent as to require washing out of the stomach. Transient vomiting is rather an advantage, since it clears not only the stomach but also the tracheobronchopulmonary apparatus. As soon as the patient desires it he may have cracked ice and water and just as often as he wants it, even if vomiting persists, since it will act as a stomach lavage. If, however, vomiting should remain too persistent fluids may then be withheld for a time.

If the cardiac action is very rapid, ice-bag on the heart may be very beneficial. If the cardiac action becomes weak, if the blood-pressure falls, strophanthus, digalen, adrenalin, are given hypodermically. If symptoms of shock appear, the usual treatment for such a condition is instituted. Blood transfusion may even become necessary.

If the patient is very restless, nervous, and suffers pain, then pantopon, codeine, and bromides, are used. If one fears hyperthyroidism or acidosis, then bicarbonate of soda, and glucose are resorted to, and the patient must be fed with fluid food as soon as possible, even the same day of the operation.

As soon as the temperature is seen rising above  $101^{\circ}$ , the patient is packed with ice-bags. If the temperature still shows a tendency to rise

and reaches  $103^{\circ}$ , the patient is covered with a rubber sheet and the whole sheet is covered with cracked ice. Following this method, the temperature usually goes down rapidly and when it is down to  $100^{\circ}$ , the ice packing is removed.

Any rise in temperature must be counteracted with ice-bags. If the temperature runs high, the patient must be literally packed in ice, as advocated by Crile. Indeed, if it is true that with each degree of rise in temperature the chemical activity within the organism increases 10 per cent, and conversely, with each degree of falling temperature, metabolism decreases 10 per cent, the indication is clear. We must reduce the temperature by all means.

It would be a mistake, however, to expect too much of this method. In one case when the temperature ascended to  $107^{\circ}$  and  $108^{\circ}$ , packing in ice was indeed successful in bringing down the temperature to  $100^{\circ}$  to  $99^{\circ}$ ,  $98^{\circ}$ , but no improvement of the patient's condition followed, and death finally ensued after four days.

Twenty-four hours after, the drain, if any has been used, is removed. If, however, the blood is still fluid, it is better to leave the drain twenty-four hours longer.

Forty-eight hours after the operation a cathartic is used, such as castor oil, salts, or citrate of magnesia. As soon as the bowels are well open, the patient is given solid food.

The thread for intradermic suture is removed eight days after.

Whenever thyroidectomy, for some reason or another, has been quite extensive, and one fears that symptoms of hypothyroidism may follow, it is well, as soon as the patient recovers from the surgical unpleasantness, to give him thyroid extract or thyroxin, in moderate doses. By so doing, it is the aim to supply to the organism the necessary thyroid secretion, without unduly taxing the little portion of the thyroid gland left at the operation. This thyroid feeding may be kept up for several weeks if deemed necessary. In the meantime, the portion of the thyroid left *in situ* undergoes hyperplasia and finally usually suffices to meet the physiological necessities.

## CHAPTER XLIX.

### ANESTHESIA.

THE ideal means of anesthesia for human surgery has not yet been found. In canine surgery, however, we can say that a sufficient amount of morphine injected subcutaneously is the ideal means to put the dogs under complete anesthesia. A few minutes after the subcutaneous injection has been made, a reflex vomiting usually takes place; then the dog quietly goes to sleep, and about one-half to one hour after, when the dose has been sufficient, the dog is so completely anesthetized and insensibility lasts so long, that any major operation can be performed without the slightest indication of pain or struggle. Even hours after the operation has been terminated the influence of the narcotic may still be active. Then gradually and slowly the dog emerges from his artificial sleep. Only exceptionally we shall find dogs which seem refractory to the influence of morphine. No ill effects remain afterward. The dose of morphine required varies, of course, with the weight of the dog and its nervous temperament, but with a little experience, one can easily tell the amount of morphine which should be used. As a rule one or two grains is all that is necessary. Even very much larger doses of the drug are not fatal to dogs. The experience of Dr. Brumley, of the Veterinary Department of the Ohio State University at Columbus, Ohio, proves this. Wishing to kill a dog, he administered to it a subcutaneous dose of several grains of morphine. When he left, the dog looked as if dead. Great was his surprise on the following morning when he came back, to find the dog gay and brisk. That day a new method for anesthetizing canines was discovered. The advantages of this method are too obvious: no need of an anesthetist, no fear of these alarming and spectacular respiratory or cardiac collapses which still too often occur with other means of anesthesia. During the entire artificial sleep the animal breathes regularly, and superficially, while the pulse remains good and strong all the way through. It is a delight. But unfortunately this method so well suited to the canine species cannot be applied to human beings. To be sure, once in a while I have met with patients so sensitive to pantopon-scopolamine anesthesia that a moderately large dose was sufficient to put them under complete and perfect general anesthesia, allowing me, for instance, to perform from start to finish the complete removal of an intrathoracic goiter without necessitating the help of any other drug. All that I can say about



it is that I have never operated under better conditions than in these cases. Unfortunately in the great majority of cases this method is insufficient. The amount of narcotic required to produce insensibility is so near the border-line of the fatal dose that to use it would jeopardize the life of the patient. Let us hope, in the meantime, that we may some day find a means to anesthetize our patients in a similar way with a drug just as effective as morphine, pantopon, etc., but deprived of their disadvantages and dangers. The ideal would be to find a means to induce general anesthesia with a safe, harmless medication injected hypodermically.

For the time being the two choice methods of anesthesia which we have at hand are: *local anesthesia* with novocain, and *general anesthesia* with chloroform, ether, and nitrous oxide. Which one of these methods should be given the preference in goiter surgery and especially in Basedow's disease? Should we use local anesthesia only or the general one? And if we decide to use general anesthesia, to what drug should we give the preference, to chloroform, to ether or to nitrous oxide? All these questions are by no means settled since the most prominent surgeons in this field are divided in their opinions.

Kocher, Riedel, Mikulicz, Berg, Ackermann and others are of the opinion that general anesthesia is dangerous on account of its liability to cause asphyxia, bronchitis, pneumonia, cardiac collapse, etc. Indeed, they say how often during general anesthesia do we not see alarming states closely resembling death? Suddenly respiration and heart action stop, the face becomes pale, livid or cyanotic, pupils become dilated, and for a few seconds, sometimes a minute, despite artificial respiration, traction of the tongue, rhythmic pressure over the thorax, etc., the function of the pulmonary and cardiac mechanism remains suspended. To be sure, life comes back but it does so slowly, and the patient's condition remains precarious throughout the operation. There can be no doubt that postoperative deaths in many instances would have been avoided if such cardiopulmonary accidents had not occurred. In Basedow's disease the majority of postoperative accidents are attributed by these authors to general anesthesia. Riedel does not hesitate to charge general anesthesia with the majority of sudden deaths. Kocher attributed his low mortality to the use of local anesthesia. For these authors the superiority of local over general anesthesia is out of the question, not only so far as the mortality is concerned, but also so far as postoperative complications are concerned.

On the other hand, Mayo, Halsted, Curtis, Garré, Ochsner, Crile and others believe that a well-conducted and well-handled general anesthesia is less apt to be followed by severe consequences than a local anesthesia. In fact, during the latter form of anesthesia, the psychic

emotions and shock may be just as marked as with general anesthesia and their consequences just as disastrous. Certainly, real harm may be done to a patient by the mental strain and physical suffering while undergoing an operation without being unconscious. With local anesthesia the operation must be done very slowly, much time must be lost in encouraging the patient, hence a prolonged operation and increased chances for surgical shock; in addition during operation, on account of the movements for defence made by the patient in order to escape pain, there is an increased venous hemorrhage. Furthermore, the yells, cries, and sometimes the insults which the patient pours out on the surgeon who is endeavoring to do his best, are very trying to the nervous system of the operator. For these reasons it will be easily understood why many surgeons prefer the use of general anesthesia. There is therefore a matter of personal cohesion and there is certainly a great deal of truth in what Ochsner says: "The patient's confidence must be gained before the administration of local anesthesia, otherwise the patient will imagine he is suffering, and this will be almost as much harm to him as actual pain. This is very largely a personal matter. Many surgeons have the full confidence of all their patients and for them it is not difficult to employ this method."

Before drawing our own conclusions let us study a little more fully the dangers connected with general anesthesia.

When the fumes of ether or chloroform are impure, or when they are inhaled too abruptly, especially if the patient is a very nervous subject, reflex accidents may occur which may prove very alarming, sometimes fatal. They may occur even with the first inhalations of the drug. They are due to an abnormally intense reflex starting in the naso-pharyngo-laryngeal mucous membrane, even before the fumes have reached the pulmonary alveoli. We know experimentally that irritation of the nasal and laryngeal mucous membrane may cause a more or less marked diminution of the number of respirations and cardiac beats; it may even produce respiratory or cardiac collapses. The centripetal routes taken by these reflexes are the branches of the trigeminus and vagus nerves. The cardiac collapse is due to a centripetal reflex from the vagus nerve which, we know, is a moderator of the cardiac apparatus. This inhibition, however, would be only a temporary one if the bulbar moderatory centers would not soon come into play and render the collapse permanent. The respiratory collapse is due to a centripetal reflex from the trigeminus, resulting finally in an inhibition of the respiratory centers.

When inhalation of the anesthetic takes place too rapidly there is at first an increased heart action which may reach 150 to 200 beats, then the heart action diminishes and finally a cardiac collapse of bulbar

origin may take place. When too much anesthetic is given paralysis of the respiratory centers takes place.

Besides these alarming symptoms there are others of less importance but nevertheless very annoying to the patient, such as coughing, increased amount of saliva due to centrifugal reflexes through the chorda tympani and the lingual nerves, etc. All these reflexes, of course, take place mostly during the early period of anesthesia, because at that time the reflex power of the nervous centers is increased; at a later period they become greatly diminished or suppressed.

General anesthesia with ether, chloroform or nitrous oxide has other disadvantages. It is accompanied by a period of excitation which is very unpleasant for the patient and for the surgeon. Furthermore, it is followed either during or after the narcosis by vomiting.

To sum up, the dangers connected with general anesthesia are more than one; to a great extent they can be eliminated if certain rules are followed. In order to avoid respiratory and cardiac collapses, the anesthetic should be *very pure*: it should be given *with extreme care, slowly, allowing plenty of air to be inhaled with the anesthetic agent*. The excitability of the patient should be diminished by a preliminary dose of *morphine*, or better, *pantopon* and *scopolamine*. Theoretically, a sufficient dose of *atropin* would be ideal, as this drug suppresses the physiological function of the cardiac moderatory apparatus, and consequently suppresses at the same time the risks of cardiac collapse. Unfortunately, this drug is too toxic, and in order to be effective the doses would have to be too large. But to return, a respiratory collapse can be avoided with a careful watching of the course of the anesthesia and the patient. If it does happen, artificial respiration made in time will remedy the accident.

The great advantage of general anesthesia with volatile narcotics, such as chloroform, ether, nitrous oxide, is that in case of necessity it can be stopped at will at any time. The patient himself is his best protection as he eliminates the poison with each respiration, whereas if the anesthetic drug is used hypodermically the drug injected cannot be withdrawn, the detoxication lasts a long time, and takes place only through the kidneys, intestines, etc.

From all that has been said, it follows that it is impossible to set down hard and rigid rules as to just what should be done in regard to anesthesia in goiter surgery. It would be ridiculous to proclaim *ex cathedra* that general anesthesia should be used, that local anesthesia should or should not be used, and *vice versa*. Here as well as in any other medical question there is *just milieu*, a happy medium.

On the other hand, there is no question, for instance, that in patients with goiters of long standing and large size, with tracheal deformations,

spells of suffocation, chronic congestion of the entire respiratory apparatus, myocarditis, arrhythmia, marked dyspnea, *general anesthesia is contraindicated*, as it would mean enormous risks for the patient. Consequently the surgeon and the patient should get together and consent, the one to perform the operation under increased difficulties, and the other to undergo the operation with a little more discomfort and pain. But fortunately the majority of patients with simple goiter are in good general health, their hearts are strong, their resistance as yet has not been impaired, and the goiter has not had time to do very much harm. Under such conditions it is really more satisfactory for everybody concerned to use general anesthesia rather than a local one.

In Basedow patients profoundly thyrotoxic with a functionally insufficient myocardium, kidneys and liver, there is no doubt, too, that *general anesthesia must be regarded as a great danger*. *Local anesthesia is the method of choice*. It must be remembered that in such cases any surgical intervention, however small it may be with no matter what form and nature of anesthesia, is dangerous; consequently, how to proceed is a matter of surgical tact, experience, sound judgment, and perhaps to a certain extent, of personal preference. I firmly believe, however, that a well-managed local anesthesia is better suited to these patients. In the other class of Basedow patients which are still safely surgical, a *well-conducted general anesthesia* carefully given and carefully watched, is the method to be chosen. In doubtful cases, especially when local anesthesia cannot be employed on account of the extreme nervous condition of the patient, a *mixed anesthesia* can be used to great advantage in the following manner: a reasonable dose of pantopon-scopolamine is given one and one-half hours prior to and repeated one-half hour before operation; then the patient is brought into the operating room and prepared for operation. Only then general anesthesia is started, just enough to "slumber away" the patient. In the meantime the field is thoroughly infiltrated with 0.5 per cent solution of novocain, a considerable quantity being used. The general anesthesia is stopped off and on; if necessary a few drops of ether are given. The patient is all the time half-awake but unconscious of pain. I think it is the safest way of handling these cases. Here, too, the great secret of success is to know how to proportion the surgical act to the condition of the patient. Too often, indeed, failures and misfortunes are charged to the anesthetic, when they recognize as the sole cause a lack of judgment and of experience on the part of the surgeon and an injudiciously performed operation, either because "the right thing has been done at the wrong time, or the wrong thing at the right time."

**Chloroform, Ether or Nitrous Oxide?**—If we resort to general anesthesia, what drug shall we use?



It is now universally conceded that *chloroform* is a dangerous anesthetic agent. The statistics of Prof. C. Andrew, made in 1880 and based on 200,893 anesthetics, gives 1 death for 2723 anesthetics with chloroform. The record of Roger Williams, of St. Bartholomew's Hospital, London, gives 10 deaths out of 12,368 anesthetics with chloroform. Gurlt out of 201,224 anesthetics found 88 cases of death. The average of these figures gives the round proportion of 1 death per 2000 anesthetics with chloroform. Very likely this average is low, as probably a great many accidents were never reported. Chloroform is toxic for the blood, as it destroys a certain number of red cells and diminishes the activity of the white cells. It is very toxic, too, for the kidneys and liver: a temporary nephritis and hepatitis not infrequently are the sequelæ of chloroform anesthesia; even a fulminating icterus in absolutely normal patients has been observed after chloroform anesthesia. Furthermore, it is profoundly toxic for the heart, and is an intense depressor of the blood-pressure. For all these reasons chloroform must be discarded in goiter surgery.

For the time being the most popular drug, not only for thyroid surgery but for any kind of surgery, is *ether*. It is the one used by such prominent surgeons as Mayo and Ochsner in America, and in Europe by Garré, Berard, and by Kocher when obliged to, in fact, by the great majority of American and European surgeons. It is the one to which I give preference. It is superior to all others in safety and range of application, its record for mortality being about 1 to 10,000.

*Nitrous oxide* anesthesia seems to be gaining every day in popularity although the death-rate from its use is higher than from the use of ether. "The shortcomings of nitrous oxide anesthesia," says Crile (*loc.cit.*), are: "It is the most difficult anesthetic to administer; its effects are fleeting; there is an imperfect relaxation of the abdominal muscles; it is more expensive than ether, and there is more venous congestion. The anesthetist must be an individual of the keenest perception of the precise condition of the patient at every moment, *i. e.*, the anesthetist must be a delicate human recording apparatus."

Charles K. Teter (*Jour. Am. Med. Assn.*, November 23, 1912, lix) says: "Nitrous oxide is contraindicated in children under five years of age, in old people in whom arteriosclerosis is present. Nitrous oxide as an anesthetic is not ideal for major surgery in patients possessing a strong, vigorous constitution, or extremely nervous temperaments, or in those addicted to drug habits or the excessive use of tobacco. In other words, any patient who requires a large amount of general anesthesia is not a good gas-oxygen subject for control, owing to the lighter form of anesthesia induced by nitrous oxide. The ideal patients for

nitrous oxide and oxygen anesthesia are the very ill, the anemic, the debilitated, those possessing a low vitality from any cause, in short, all cases except those requiring a powerful anesthetic agent."

### LOCAL ANESTHESIA.

Eggleston-Hatcher, in 1919, found that when large fractions of the minimal fatal doses are injected intravenously at intervals of from fifteen to twenty minutes, or when relatively dilute solutions of the drug are injected slowly and continuously, the several drugs can be divided into two groups based on the difference in their rates of elimination. Group I includes alypsin, apothetin, betaeucain, nirvanin, procain (novocain), stovain and tropacocain, all of which are rapidly eliminated, so that several times the minimal fatal dose of any of these can be injected in the ways just mentioned in periods of one or two hours without causing the death of the animal. Group II includes cocaine and holocain, which are much less rapidly eliminated, and which, therefore, cause death in much smaller total doses when given as described.

When injected subcutaneously into cats, the local anesthetics can again be divided into the same two groups, depending on their rates of elimination. All are apparently absorbed rapidly, but those of Group II are much more toxic by subcutaneous injection than those of Group I, because their elimination is not rapid enough to keep pace with their absorption. Five or more times the minimal fatal vein dose of any of the members of Group I can be injected subcutaneously without causing death, while less than four times the fatal vein doses of those of Group II prove fatal.

When absorption from the subcutaneous tissues is delayed by the simultaneous injection of epinephrin, the difference between the two groups is emphasized, and the toxicity of the members of the first group is reduced far more than that of the members of the second group. The elimination of members of Group I proceeds at the rate of at least one fatal vein dose every twenty minutes, while not all of a subcutaneous dose of cocaine, one and one-third times that fatal by vein, may be eliminated in twenty-four hours or more.

The elimination of all the local anesthetics is accomplished almost entirely by their destruction in the liver, as can be demonstrated by perfusion of the excised, surviving organ with diluted blood containing large quantities of the drug in solution, and subsequent determinations of the amount remaining in the perfused fluid.

The symptoms produced in cats by toxic doses of the various local anesthetics are essentially alike, and they are also essentially the same as those observed in man. All of these drugs kill by simultaneous paralysis

of the heart and the respiratory center. Eggleston-Hatcher therefore tried artificial respiration in cats as a resuscitative measure, with and without cardiac massage, but it proved ineffective even when combined with massage of the heart.

The employment of artificial respiration in combination with stimulation of the heart by the immediate intravenous injection of epinephrin, however, enabled them to resuscitate the majority of cats after the rapid intravenous injection of doses of the local anesthetics up to twice the fatal dose. Since the heart had stopped in most of the cats, it was necessary to practice massage of the heart in order to bring the epinephrin into contact with it. The success of this method of resuscitation depends on the rapid destruction of the local anesthetics, whereby the excess administered, is promptly eliminated if the circulation can be maintained for only a few minutes by the stimulation of the heart with epinephrin. But even with such stimulation, and even when it is evidently recovering, the animal will die of respiratory paralysis unless the center is supported for a few minutes by artificial respiration.

It is evident, therefore, that if the circulation and respiration can be maintained for a few minutes, the rapid destruction of the local anesthetics by the liver will care for amounts considerably in excess of those which are usually fatal. The close analogies between the behavior of man and cats to toxic doses of the local anesthetics, and the fact that man also recovers rapidly from the effects of non-fatal doses, suggest that he also accomplishes their elimination or destruction in the liver, and it seems highly probable that the use of epinephrin and artificial respiration will prove effective as resuscitative measures in many cases of acute poisoning in man.

In conclusion, it may be said that the best way to combat acute poisoning from drugs employed for local anesthesia are:

1. Cardiac massage.
2. Artificial respiration.
3. Intravenous injection of epinephrin.

It follows, furthermore, that as a preventive measure, it is well to add epinephrin to any of these drugs, when used hypodermically.

Cocaine is still the most powerful among the local anesthetics, but its toxicity forbids its being used too freely. The drug of choice for local anesthesia for the time being is *novocain*. It possesses a far more superior anesthetizing power than stovain, tropococain, and about an equal power with cocaine. On the other hand, novocain is twice less toxic than cocaine. The injection of 0.5 per cent solution hypodermically is slightly painful if novocain is dissolved in simple water, but becomes absolutely painless if dissolved in normal salt solution. Anesthesia with novocain is complete eight to ten minutes after the injection has been made and

is nearly always perfect in the injected area. It lasts about half an hour. The period of anesthesia may be prolonged by adding adrenalin to the novocain solution. The following formula is the one which gives the best results:

Salt solution . . . . .	100.0 gm.
Novocain . . . . .	0.5 "
Adrenalin 1:1000 . . . . .	25 drops.

If a 2 cc syringe is used for injection, each syringe contains 0.01 gm. of novocain and one-half drop of solution of adrenalin 1:1000. This mixture of novocain-adrenalin possesses a powerful anesthetizing capacity which is about equal to that of cocaine; its effects last about an hour. It is absolutely painless, and while novocain alone has no effect upon the bloodvessels, the mixture, novocain-adrenalin, causes a pronounced vasoconstriction lasting several hours. The adjunction of adrenalin does not increase the toxicity of the drug, consequently large doses of the solution can be used in the same patient. Chaput, using it for the removal of a cancer of the breast, went so far as to use 140 cc of 0.5 per cent solution. No ill effects were observed.

It must be always remembered that the mixture novocain-adrenalin does not keep very long. *It must be freshly prepared each time before using it.* Inasmuch as a solution of novocain, just as that of adrenalin, kept separately keeps perfectly for a long time, it is better to have both at hand always separately prepared and to mix them only just before the operation. The novocain solution can be sterilized at the autoclave without injuring its anesthetizing properties. So far as adrenalin is concerned, we have the choice between the *adrenalin* itself, which is extracted from the suprarenal bodies, and the one synthetically obtained and called *suprarenin*. Theoretically, suprarenin offers greater advantages than adrenalin. Being synthetically prepared, it is always identical with itself, consequently its properties are constant. Furthermore, it can be sterilized with impunity at the autoclave, whereas adrenalin is readily oxidized and when sterilized loses a great part of its properties. The oxidation and consequently the deterioration of the solution are recognized by the fact that the solution becomes pink, then red and finally brown in color. *Adrenalin chloride*, however, which is an additional product formed by the action of dilute hydrochloric acid upon adrenalin, seems to be a quite stable product. When in ampoules, according to Rowe, it may be heated to the temperature of boiling water, and can be sterilized several times in succession without loss of activity. When exposed to the air, it may be sterilized twice without loss of activity.



There are on the market small tablets of novocain and adrenalin already mixed in the desired proportions. These tablets, of course, are of the greatest convenience, but according to Piquand, they are far from having the same anesthetizing power that is possessed by a mixture prepared on the spot just before the operation.



FIG. 94.—Local anesthesia. The picture shows a row of intrademic blebs along the line of future low-collar incision. The picture shows, furthermore, where the injection will have to be made in the prethyroid muscles after the two skin flaps have been retracted before undertaking their division.

Local anesthesia should never be employed unless the patient is lying down. If the injection is made in the sitting posture, collapse is liable to take place. This is not at all to be wondered at when we know that the injected solution of novocain-adrenalin does not exert its action locally only, but that to a certain extent its influence extends to the entire organism. As adrenalin is one of the most powerful vasoconstrictive drugs, vasoconstriction takes place in the brain, producing cere-

bral anemia, and hence collapse. If the patient is in the dorsal decubitus, the chances for collapse are less marked, since the lying posture favors congestion of the brain. Before using local anesthesia it is prudent whenever it is possible to give a dose of pantopon and scopolamine half an hour before. Scopolamine being a vasodilatatory is especially indicated in local anesthesia, as it more or less counterbalances the general effects of adrenalin.

**Technic of Local Anesthesia.**—Although apparently simple, this technic requires skill and experience. When once the course of the future incision is decided upon, one of its ends, the nearest to the surgeon, is seized between the thumb and index finger of the left hand so as



FIG. 95.—Local anesthesia. Local anesthetic is injected into the whole field of operation in order to render anesthesia as perfect as possible.

to form a thin, cutaneous fold, which is then lifted. The fine needle of a syringe loaded with 0.5 per cent solution of novocain-adrenalin is inserted *into the derm* of the skin and *not in the subcutaneous tissue*. A small quantity of the anesthetic is then forced into it. At once it forms a white bleb 1 cm. in diameter, which is the best proof that the injection is really intradermic. The needle is then pushed forward, and while pushing, a continuous pressure upon the piston of the syringe forces continuously some of the anesthetic solution into the tissues, thus rendering the injection painless.

A well-managed local anesthesia should cause only at one time a

little pain, and that is when the needle goes through the skin for the first time. Then the patient should be warned that he is going to feel a pricking pain. In the subsequent injections, as the needle goes through the anesthetized area, no pain should be felt. These intradermic injections are repeated until the entire line of the future incision forms a continuous row of blebs from 1 to 2 cm. in width (Fig. 94).

When once the site of the future incision has been thoroughly anesthetized, subcutaneous injections of novocain-adrenalin are made along the same course. Then the anesthetizing solution is forced into the entire subcutaneous region above and below the incision, not only where the upper and lower flap will be dissected but also in the entire region



FIG. 96.—3 and 5 are made not only subcutaneously but also deeply behind the sternocleidomastoid muscle so as to reach the bulk of the superficial cervical plexus.

neighboring on the field of operation (Figs. 95 and 96), as the sternocleidomastoid region, the thyroid cartilage region, etc. The more perfect the infiltration of the cervical region with the anesthetizing solution the less will be felt the pain during operative manipulations.

Eight to ten minutes should elapse before the incision is made. Only then the incision and the preparation of the upper and lower flaps can be made without pain.

The upper and lower flaps being retracted the cervical fascia and its underlying muscles are then infiltrated with novocain-adrenalin solution, especially at the point where the incision will take place (Fig. 94). As the thyroid is not sensitive it will not be necessary to inject

any anesthetic into it. The two regions where some pain is felt are the upper and lower poles. They are consequently thoroughly anesthetized with the mixture. Before luxating the goiter, as this part of the operation is very painful, it is well to inject some novocain-adrenalin solution into the surgical capsule. The same must be done, too, around the trachea and esophagus and on the posterior surface of the thyroid (Fig. 97), bearing, however, in mind the danger zone. When dealing with the isthmus, novocain-adrenalin solution must be injected above and below the isthmus and between the latter organ and the trachea (Fig. 97).

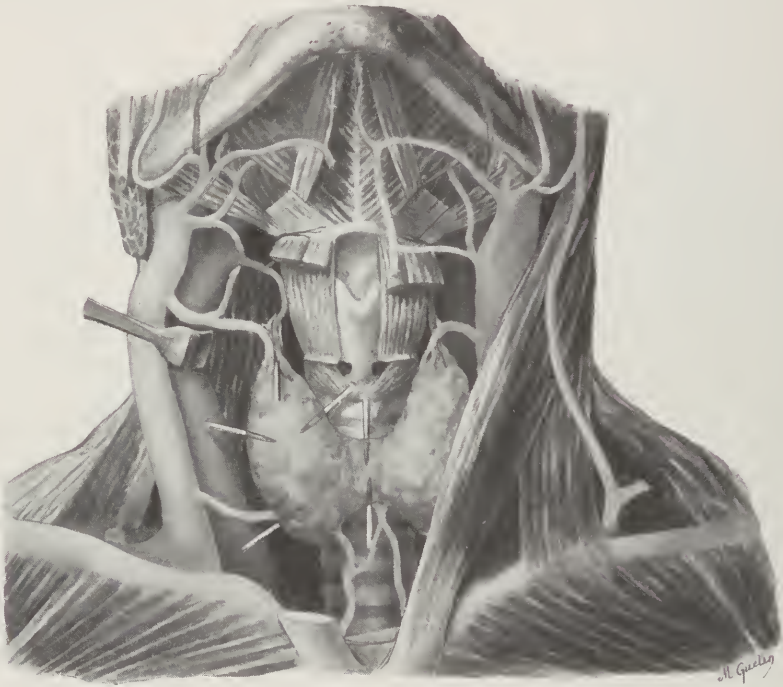


FIG. 97.—Local anesthesia. Showing how and where to inject the local anesthetic in order to fully anesthetize the deep tissues.

If one follows carefully the three following rules, local anesthesia will give in a great many instances very satisfactory results.

1. One should wait eight to ten minutes after infiltration is completed before beginning the operation.

2. The surgeon should always keep within the limits traced by the injection. As soon as he steps outside of these limits pain is sure to follow.

3. Operation should be done carefully, methodically, with gentleness. Roughness does not agree with local anesthesia. In this respect



the assistants with their retractors, if not intelligently controlled, can do a great deal of harm.

**Intratracheal Insufflation Anesthesia in Thyroid Surgery** seemed at first to be full of promise. I have, however, found it disappointing. Just in the cases where it was expected to be the most useful, namely, in goiters with pressure symptoms, it failed to fulfil its expectations.

1. As is known, before the intratracheal insufflation can be used the patient must be put to sleep in the usual way. It is only when the patient is anesthetized that the catheter is passed into the trachea. Now, then, in goiter causing pressure symptoms, suffocation, as a rule, occurs with the first inhalations of ether, so that one has no time to resort to the intratracheal insufflation method; the operation must be very quickly done in order to relieve pressure upon the trachea, or tracheotomy must be performed *a tout prix*—at all costs—otherwise the patient will be dead; consequently the object of intratracheal insufflation is defeated.

2. Since in order to pass the catheter into the trachea the head must be excessively extended, if the pressure symptoms are already marked, suffocation is bound to be made much worse by the hyperextension of the head, hence the necessity to pass quickly the catheter into the larynx. This is not always easy. I confess that in some of these distressing moments I have failed. Mucus is so abundant and congestion is so marked that the process is not an easy matter by any means. Add to it all that the time you have at your disposal is so short that you are confronted with the dilemma: either to pass the tube or to let the patient die. Each second lost in the attempt means that much less time left to reach the windpipe by the cervical route through an incision, if the catheter cannot be passed into the trachea. Knowing that after thyroidectomy a thymic dyspnea is liable to occur most unexpectedly, I always have the intratracheal insufflation apparatus in the room of the patient ready for an emergency. In 3 cases where I had such accidents I failed to pass the tube into the trachea.

3. If the trachea is displaced and compressed, the catheter often cannot be made to pass the point of compression.

4. Robinson collected 1400 cases of intratracheal anesthesia with 7 deaths, 1 from lung rupture and 1 from emphysema.

**Pantopon-scopolamin.**—Nowadays anesthesia, be it general or local, is obtained through a *mixed narcosis*: a preliminary dose of a hypnotic of some sort is given hypodermically before; and the effect of this adds to that of the subsequent drug used for general anesthesia. Up to now morphine has had the priority; lately, however, *pantopon* seems to take its place very advantageously.

Pantopon is superior to morphine for many reasons: It contains the totality of the useful alkaloids of opium soluble in water, and it can be

injected hypodermically just as well as morphine. No doubt morphine possesses the analgesic and hypnotic properties of opium; but opium owing to the presence of its various alkaloids possesses other secondary actions which morphine has not. For instance, it has a sedative action over the nervous system, a tonic influence over the cardiac system, and an antinauseous effect which morphine certainly has not. Pantopon may be regarded as a purified opium. All the harmful alkaloids have been eliminated and the useful retained. Roughly speaking, pantopon contains 50 per cent of morphine, 20 per cent of narcotin, 2 per cent of codein and papaverin, and 1 per cent of thebain and narcein. This drug has been advocated by Sahli, of Berne, in collaboration with Scharges.

In equivalent doses, morphine may be slightly more analgesic and probably has a more rapid action, but the digestive tolerance of pantopon is far superior. Vomiting after the use of pantopon is less frequent than after the use of morphine. The tonic influence over the cardiac system is manifest with pantopon. The paralytic influence of morphine is well known; according to Wertheimer, Löwy and Bergeim, the paralytic influence of pantopon on the respiratory centers is far less accentuated.

After pantopon has been given hypodermically in association with scopolamin, the patient falls into a dozing sleep—the “*Dämmerschlaf*” of the Germans. The active movements cease; the sensation of pain is diminished to a great extent; consciousness although still present is considerably reduced; the patient sleeps, but may be awakened by call, light or sound. In some instances the patient is so thoroughly anesthetized that a complete operation may be performed without his knowledge. Naturally, such results vary with the doses employed and the individual’s sensibility. I have seen, although not frequently, patients who did not respond to the action of pantopon and to whom morphine had to be given instead. They were nervous, mostly thyrotoxic patients, in whom the cerebrospinal system was greatly excited. However, this lack of response happens with morphine, too. As a rule, women react more readily than men, consequently smaller doses of pantopon may be given to them. Pantopon may be given to children as well, without any danger.

To sum up, pantopon-scopolamin in surgical work seems to have great superiority over the morphine-scopolamin combination. It diminishes the vomiting to a great extent during and after the operation. It reduces materially the quantity of the drug used to induce general anesthesia and diminishes the preanesthetic excitation period. It has not the same constipating effect on the intestines as morphine. The average dose is from 2 to 4 cgm. of pantopon and from 0.0003 to 0.0005 cgm. of scopolamin. As a general rule we can say that the dose of pantopon which must be employed is about double the one of morphine;

consequently in cases where 1 cgm. of morphine would be given, 2 cgm. of pantopon will be necessary to obtain the corresponding effect.

One must be careful in the handling of scopolamin. It is best to have the solution freshly prepared each time before using. Pantopon and scopolamin may be given simultaneously or separately. However, the majority of authors claim that it is better to give them separately and at intervals of one-half hour.

In goiter surgery pantopon-scopolamin is used to the best advantage in the following manner:  $\frac{3}{4}$  of a grain of pantopon and  $\frac{1}{150}$  grain of scopolamin are given one-half hour before operation. If a patient shows an idiosyncrasy to the drug, the operation must be postponed a day or two in order to permit elimination. I have been using pantopon-scopolamin for nine years now and have not met with such a necessity.

No medicament is ideal and the pantopon-scopolamin combination has its weak points, too. As said before, in alcoholic and Basedow patients, instead of producing a sedative effect on the nervous system it may, on the contrary, cause an excitement of it; this is rare, however, and also happens with morphine. After the use of pantopon-scopolamin the patient often complains of dry mouth and thirst. This sensation is not due to pantopon but to the scopolamin, since we know that the latter drug influences the terminal ends of the secretory nerves. This action is purposely counted upon in giving ether anesthetic, as it prevents the troublesome formation of mucus in the bronchotracheal tract. The really greatest danger of pantopon-scopolamin is its liability of causing a paralysis of the respiratory centers. As said before, this liability is less marked for pantopon than for morphine. Large doses should not be used in weak people, in old patients, and in those with disturbances of the respiratory apparatus.

## CHAPTER L.

### POSTOPERATIVE COMPLICATIONS.

**Shock.**—The phenomenon known as shock was a condition recognized as early as 1568 by Clowes, and by Weismann in 1719, who spoke of it as a condition probably caused by the presence of a foreign body in the wound or blood. The word “shock” was first used clinically in the eighteenth century and was meant to express the notion of grave organic disturbances unaccompanied by demonstrable organic changes. It is difficult, not to say impossible, to give a clear, concise and correct definition of shock. The word does not represent a definite symptom, but a symptom-complex dependent upon more than one causative factor. The best definition of shock which I know of is the one given by the elder Gross when he said, “Shock is the rude unhinging of the entire machinery of life.” Clinically, we call shock a condition characterized by a low blood-pressure, a soft, rapid, and thready pulse, a marked pallor of the mucous membrane and integuments, a rapid and superficial, and often irregular respiration, air hunger, subnormal temperature, cold and moist extremities and finally a more or less marked degree of stupor, with diminished or suppressed sensibility to painful stimuli; sometimes there is mental anxiety without outcry. It is an error to make a difference between shock and collapse: they are the same thing.

In the last few decades explanations and theories have succeeded one after the other, each one trying to locate the “unhinging” at the door of some organ or function, but everyone of these theories has failed to solve the problem. The most important theories regarding shock are:

1. Vasomotor exhaustion and paralysis.
2. Cardiac spasm and eventual failure.
3. Inhibition of the function of all the organs.
4. Deficiency of carbon dioxide in the blood, or acapnia.
5. Morphological changes in the ganglion cells.
6. Loss of vasomotor control due to inhibition from afferent sensory influences.
7. Primary suprarenal exhaustion.

1. **Vasomotor Exhaustion and Paralysis.**—Nearly half a century ago Keen, Mitchell, Moorehouse and Fischer advanced the theory of vasomotor exhaustion with flooding of the splanchnic veins and contraction



of the peripheral vascular system. This theory was, for a time, rejuvenated by Crile. He argued, "that the essential phenomenon of shock was low blood-pressure, that since there was no demonstrable lesion in fatal cases and no later effects in those who recover, we must assume exhaustion rather than structural lesions to be the cause of this fall." This exhaustion is not located in the heart. The accelerated heart action must be taken as evidence of the effort of the regulating centers to recover the lost blood-pressure. The splendid action of the heart under these conditions after infusion of the salt solution proves it to be well capable of further action. This exhaustion is located neither in the cardio-inhibitory nor in the cardio-acceleratory centers, as shock may occur even when the cardiac nerve supply, namely, the vagi and sympathetic branches have been severed. The peripheral nerve vascular mechanism cannot be incriminated, as it responds to stimulants always. Finally, the vasomotor centers are not exhausted either because these centers respond to electric stimulation even when the organism is in a state of profound shock. Porter and Quimby showed that the central end of the sciatic nerve can be stimulated for hours without causing any fall of pressure. On purely empirical grounds Malcolm, of England, claimed that the vasomotor centers not only were not exhausted, but were overactive throughout shock, and that the peripheral vascular system instead of being relaxed was contracted. He based his conclusions on the fact that in shock the surface of the body is cold, the skin pale, the pulse small, the mucous membrane blanched, and the bleeding from the wound surface scant. Sheen very judiciously remarked that in shock an unduly large proportion of blood was in the abdomen. According to Janeway and Ewing, it is "as though the branches of the mesenteric arteries emptied into a large reservoir with perfectly flaccid walls, into which they bled to death. The aptness of the comparison of the splanchnic area to a flaccid rubber bag is made more apparent by pressure on the abdomen: the blood-pressure can be raised at will by this procedure." This will explain why the peripheral vessels are small. Henderson claimed that "in shock the vasomotor center does its full duty almost to the last; the fall in blood-pressure is due to the diminution of the volume by transudation of its fluid constituents out of the vessels into the tissues." In his experiments on dogs, he noticed that they died of "respiratory failure long before pressure had become very low." This, I have experienced clinically, too, in one of my patients who died in a state of profound shock after thyroidectomy performed under local anesthesia. In that case respiration had stopped a long time before cardiac action had ceased. Seelig and Lyon very elegantly demonstrated that in normal animals stimulation of the central end of the vagus nerve when divided causes a rise in blood-pressure and that

this rise occurs even when the animals are in the most profound degree of shock, thus showing that the vasomotor centers are still capable of activity. We must consequently admit that low blood-pressure is an important accompanying symptom of shock, but that it is not the primary cause of it.

2. **Cardiac Spasm and Eventual Failure.**—Boise attempted to prove that, on account of peripheral trauma, the heart is overstimulated and thrown into spasm, hence an increased systole, and decreased diastole, a lessened output of blood from the heart, and consequently a lowered pressure. As Seelig says, Boise fails to explain why the work of numerous investigators who have thoroughly isolated the heart from its afferent paths have still been able to produce shock.

3. **Inhibition of the Function of all Organs.**—Meltzer, reviewing all the more recent theories of the nature of shock, ventures the assumption "that various injuries which are capable of bringing on shock do so by the inhibition of all the functions of the body." Differing from Crile, he quite justly questions the legitimacy of distinguishing etiologically between shock and collapse. He fails, however, to give satisfactory proof of his theory of shock.

4. **Deficiency of Carbon Dioxide in the Blood, or Acapnia.**—Henderson thought that shock was due to a deficiency of carbon dioxide in the blood on account of the rapid and deep breathing induced by traumatism, so causing an undue ventilation of the lungs resulting in a condition of overoxygenation of the blood with diminished carbon dioxide or *acapnia*. Carbon dioxide is not merely a poisonous excretion, but is an important regulatory hormone upon whose presence depends the activity of the respiratory centers. According to Henderson the tonicity of the walls of the bloodvessels is in direct proportion to the carbon dioxide content of the blood. This doctrine of *acapnia* is clinically untenable, as in the great majority of cases of shock excessive ventilation of the lungs cannot be regarded as a causative factor. Howell demonstrated that the heart still beats in complete *acapnia*, and Seelig found that by introducing directly carbon dioxide into the blood current, he could not influence the course of shock.

5. **Morphological Changes in the Ganglion Cells.**—Crile explains shock by the *exhaustion theory*. According to him, the brain is a great storage battery in the kinetic system, driving the suprarenal, the muscles, and through its action on the suprarenal, the other important viscera. In his judgment all forms of shock are caused by overstimulation of the nervous system, and finally by exhaustion. Basing his theory upon study of the phylogenetic history of the whole motor mechanism, he claimed that when there is no response to nervous stimulation, the energy is expended in the cortical cells. The brain cells then show

physical changes which vary with the stage of shock in which they are examined. He found in the brain cells hyperchromatic stages followed by hypochromatic ones. In his judgment these demonstrable, constant morphological alterations of the brain cells are the primary cause of shock. This, he thinks, he has been able to demonstrate by an enormous amount of experimental work done in the numerous and various states and conditions. The brain cells studied were almost entirely those of the cerebellum (Purkinje cells). As Seelig says, "The essence of his doctrine lies in the brief that the cells are composed of labile compounds capable, when adequately stimulated, of converting their potential energy into kinetic. If this power to convert is unduly excited, phenomena of exhaustion with all their consequences occur."

Gray and Parson, two English authors who have worked along the same line as Crile, most definitely and emphatically state that the most careful histological examination of the brains and spinal cords of shocked animals fails to reveal any changes in the ganglion cells as described by Crile and Dolly. In the spinal cords they found no cytolytic changes whatever. The spinal cortex showed very little change and the Purkinje cells showed no striking alterations. They concluded that in shock the exhaustion theory cannot be proved histologically.

Mann claims that it is impossible to reduce the anesthetized animal to a state of shock by any degree of sensory stimulation, provided all hemorrhage is prevented and its abdomen not opened.

Since the same pathological changes as the ones described by Crile are found in other conditions than shock, as overwork, anemia, infection, poisoning, Graves's disease, etc., these changes are not in the least considered by many as specific of any etiological factor, nor are they specific for shock. Seelig says: "The theory of ganglion-cell excitation as the primary cause of shock stands as the type of solidistic pathology. Virchow has characterized all solidistic theories in pathology (as contrasted with humoral theories) as metaphysical and speculative; and in this statement resides the crux of the problem. Crile may encounter no difficulty in showing that the condition of shock has definite morphological representation in the ganglion cells of the cerebellum, but he frequently approaches dangerously near the borderline of speculative metaphysical reasoning in his attempt to prove that these same morphological changes are the primary cause of shock."

6. **Loss of Vasomotor Control.**—Janeway and Ewing claim that shock is due to loss of vasomotor control caused by inhibition from afferent sensory impulses. To prove their contention they have undertaken a series of very interesting experiments. But through what mechanism this condition is brought about is not explained by them.

7. **Primary Suprarenal Exhaustion.**—Finally, the last theory of shock up to date is the one of Corbett: primary suprarenal exhaustion is a shock factor. Corbett says: (*loc. cit.*) "The amount of epinephrin in the blood of a normal individual is very slight, somewhere between one part in two hundred millions as determined by Hoskins, and one part in ten millions as determined by Waterman and Smith. Further than this, the epinephrin output per minute per kilogram of dog cannot be above 0.2 cc of a 1 : 1,000,000 solution of epinephrin. The smallest amount of epinephrin that will have any effect upon the blood-pressure of a normal dog is 0.42 cc of the same solution. This amount produces not a rise but a fall in the blood-pressure, and the amount necessary to produce a rise is several times as much. These facts indicate that in the normal individual just enough epinephrin is in circulation to maintain the tone of the 'myoneural junction,' as the pegs of a violin maintain the tension of the strings. Therefore we have no right to say that the normal blood-pressure is maintained by epinephrin in the blood, but rather that epinephrin *sensitizes unstriated muscles of the vasomotor system to the sympathetic.*"

Furthermore, the splanchnic nerves must also be intact in order to have function of the suprarenal glands, as shown by Cannon, Dreyer and Elliot. Peritoneal traumatism, stimulation of the sciatic as shown by Elliot, reduce not only the epinephrin output, but also actually reduces the epinephrin content of the glands. After a number of experiments Corbett comes to the conclusion that symptoms of shock fully develop only after the supply of epinephrin is greatly depleted. Epinephrin exhaustion is a shock factor.

Such are the theories. Everyone of them sees a part of the truth, but none of them explains the problem of shock fully. Shock is a composite of various factors. It seems to me, however, that Crile is on the right track, when he requires for the production of shock the intervention of the nervous system, whatever form it may take, but takes things too much for granted when he concludes that the morphological changes in nervous cells are the primary cause of shock. How far have we the right to take the cells' morphology as an index of their functional activity? Most probably in the course of future researches and when our knowledge of biological chemistry is more advanced, we may find the solution of the problem in the pathological biológico-chemical interrelations not only of the nervous system, but also of the entire apparatus of internal secretion. What would tend to prove that my contentions are correct, is the fact that shock can be nearly always successfully handled if a sufficient amount of new blood is transfused. This has been elegantly shown by Janeway and Ewing. These authors saw dogs so deeply shocked that the controls similarly shocked died, immediately



resuscitated by blood transfusion. Why should it be so if the primary cause of shock is to be found in the morphological lesions of the nervous system? So rapid a recovery precludes the idea that the disturbing factor is due to an exhaustion of the nerve centers. It is hard to conceive an exhausted center recovering so quickly. It seems reasonable to admit that the new blood transfusion brings "something" which is no longer, or which is insufficiently present, in the system of the shocked animal, and which when reintroduced into the organism, sets going all the machinery, just as a few drops of HCl will set going again an exhausted electric battery. What this something can be, I know not. Perhaps as Corbett says, the epinephrin; perhaps a glandular secretion of some other sort, or one or more lipoids, or one or more biogicochemical-compounds, whose chief duty is to stimulate the nervous centers, or possibly some others of the organs of internal secretion. Not enough attention so far has been paid to the organs of internal secretion, as to their possible etiological relation to shock.

We know that these organs contain a great number of lipoids, each one of them possessing individual physiological properties. Certainly lipoids must not be the only compounds which intervene in the complicated biological chemistry of our body; there are and must be others, and most probably it will be only when we know more of the science, still in its infancy, namely, *biological chemistry*, that we shall get a little nearer the solution of the problem of shock.

Shock may be of *psychic, traumatic, toxic and hemorrhagic origin*.

It is quite certain from clinical observations that shock may follow *psychic* disturbances without any definite trauma, toxin, and loss of blood. This psychic shock is mostly caused by fear and anxiety. This psychic factor is a very important one, and it is often not given sufficient consideration. It varies with the individual, with sex, with age, race, and social condition. The fear of an impending operation is sometimes considerable, and it is indeed the duty of the physician and surgeon to alleviate this fear as much as possible.

*Traumatic shock* in accidental injuries has been known for many years. Shock connected with operation seems to recognize the same causes as the ones seen in accidental injuries. For a long time surgeons have felt that if the patient is generally anesthetized, the operative manipulations on the unconscious patient may be done with impunity. Crile has taken the opposite stand and claims that even during artificial sleep, painful impulses from the wound to the brain are taking place, are registered there just the same, but are not felt, as the entire sensitive apparatus is anesthetized. These noxious impulses, he says, are a contributory factor of shock; they increase the probability of post-operative complications, increase the discomforts of the convalescence

and prolong the period of disability, and they should consequently be eliminated as much as possible. Hence the origin of the *anoci-association theory* of Crile. He aims to prevent shock by sequestering the brain from the field of operation by blocking the nerves with novocain. I have expressed elsewhere my views on this subject.

*Toxic shock* may be seen in diseases of long standing, as thyrotoxicosis, typhoid, acute and intestinal obstruction, jaundice, certain stages of diabetes, etc. It is seen, too, after the use of drugs for local and general anesthesia.

*Hemorrhagic shock* is seen after severe hemorrhages either previous to, during, or after operation. Many or all of these different factors, as a rule, are combined in order to produce shock. One factor seldom acts alone.

**Treatment of Shock and Hemorrhage.**—Prevention is, of course, the best method of treatment. It is clear that if it is true that during general anesthesia, nocuous impulses are nevertheless transmitted to the brain in such a way as to jeopardize the life of the patient, something should be done to prevent that risk. Consequently, if one believes in Crile's theory of shock and in his anoci-association theory, to be consistent with himself, he will have to employ the methods which Crile advocates in order to prevent shock. And this I did for three years. But, as said before, when the last great war broke out, as novocain could not be had any longer, I felt forced to give up the anoci-association method. Despite that fact I have been unable to see any difference for the worse in my results. So, until further convincing proof, I have discarded the use of novocain.

The necessity of eliminating as much as possible the factor of fear is self-evident and this can be done by the most careful coöperation on the part of the nursing and operating staff. It may be reduced to a great extent, too, by the intelligent use of morphine or pantopon. As claimed by Crile, general anesthesia should be administered very carefully, taking care to prevent loss of body heat, and to avoid hemorrhage during operation; furthermore, the tissues should be handled carefully, without roughness, and the operation should be performed with such speed as is commensurate with the safety of the patient.

It would be an error, however, to believe that because one has blocked the nerves, has eliminated the factor of fear, has used nitrous oxide, etc., in short, has applied the method of anoci-association, that he is safe in undertaking any operation on a patient, and that he may be sure that the outcome will be all right. This, indeed, is not so. The best anoci-association method I know of is a *sound surgical judgment*. As already said more than once, the judgment and experience of the surgeon will, I think, determine very largely the outcome of each given

case. We have killed a great many patients with exophthalmic and other forms of goiter because we have done too much, because we have used a general anesthesia when local anesthesia should have been used, because we have subjected them to an operation near or at the top of a wave of hyperthyroidism, because, in other words, we have done "the right thing at the wrong time, or the wrong thing at the right time. There is possibly no other field in surgery where it is truer than in thyroid surgery that the surgeon must be, not only a good technician, but also a most capable physician, competent to appreciate the strength of the heart, to judge how much shock a nervous system will stand and how much it will not, to know if the case is complicated with thymus enlargement or not, and to decide if the degenerative processes of the organs have gone so far as to compromise the success of the operation, or if they will stand the strain. Even with the best medico-surgical judgment and with wide experience every surgeon will meet with misfortunes because the conditions found are very deceiving. A heart seems to respond beautifully to a preliminary treatment, but great is the disappointment when you expect this heart to stand by you, to find that it simply 'quits.' That is why I believe Crile is not doing himself justice, and is giving too much credit to his anoci-association theory, when he attributes the good results mostly to this method. Ten, five, yes, even two years ago, the technic, the indications, the conception of the operations, were not in many respects what they are today, and very likely in a few years from now they will have advanced and changed again. Our experience becomes every day larger, and with it improves our surgical judgment. Every day we learn better what to do, what not to do, how far to go, and how far not to go. How could it be otherwise? What shall we say of Kocher, who systematically used local anesthesia in his goiter work, who did not make a point of eliminating the factor of fear, whose patients knew beforehand the day and the very hour of their operation, and who even walked to the operating table? Everyone of us knows that an operation performed under local anesthesia is not as painless as one would wish it, consequently the nocuous impulses toward the brain are still extremely active and harmful, yet who can criticise Kocher's results, not only so far as mortality, but so far as immediate and remote results are concerned? I think Bevan is quite correct when he says, 'Crile's excellent surgical work is done not because of anoci-association, but in spite of it.' "

When shock takes place during the operation, the anesthetic should be stopped at once, and the operation interrupted if possible. Then if a two-staged operation can be devised, it is far better to do so. If not, as much as possible of the operation must be done under local anesthesia.

When shock is already established, it is treated in the following

manner: the extremities are bandaged; the foot of the bed or operating table is elevated; heat is applied if the patient is cold; ice to the head in hot weather, or if the patient has temperature. If tachycardia is very marked an ice-bag is applied to the cardiac region. If the patient is very restless, small doses of morphine may be given with benefit. If shock is only moderate, proctoclysis by the drop method with the following solution should be started at once.

Sodium chloride . . . . .	6.0 grams
Calcium chloride . . . . .	1.0 "
Potassium chloride . . . . .	0.3 "
Bicarbonate of soda . . . . .	60.0 "
Glucose . . . . .	150.0 "
Alcohol . . . . .	20.0 "
Aq. dest. . . . .	1000.0 cc

This should not be given in too great quantities at a time, but should be repeated at intervals, and given slowly. This solution increases the pressure in the vena cava, and since the output of the heart is in direct proportion to the pressure in the vena cava and not at all to the aortic pressure, rectal infusions at once increase the blood-pressure and the volume of the pulse.

Hypodermoclysis is best made underneath the breast or in the axilla. If for any reason the thorax must be avoided, the space of Retzius can be used advantageously.

If, however, one is in need of more quickly acting methods, intravenous infusion must be resorted to at once. The best solution to use is the Locke-Ringer, which is far superior to the salt solution commonly used up to date. The Locke solution has been employed for a number of years in laboratories not only as a means of keeping up artificial circulation in experimental work, but also as a medium to preserve the life and excitability of the tissues coming from the liver, intestines, ureter, etc. Its composition is the following:

Sodium chloride . . . . .	8.0 grams
Calcium chloride (non-crystallized) . . . . .	0.2 gram
(if crystallized) . . . . .	0.4 "
Potassium chloride . . . . .	0.2 "
Bicarbonate of soda . . . . .	0.2 "
Dextrose (purified) . . . . .	1.0 "
Aq. dest. . . . .	1000.0 cc
Oxygen, enough to saturate.	

The Locke solution is preserved in sterile bottles and the whole sterilized anew at the autoclave. The chemical products entering into



the formula must be chemically pure. The oxygen which is a necessary condition for experimental work when producing artificial circulation is no longer necessary when used clinically for transfusion.

The sodium chloride is used in order to give the liquid the osmotic property equal to the one of the blood, so that the hemoglobin will remain fixed to the red corpuscles, in other words, in order to prevent hemolysis. The calcium is necessary to keep up the function of the heart and the potassium is intended to regulate the function of the cardiac fibers. The bicarbonate of soda is necessary in order to confer to the liquid about the same alkalinity as the blood. Glucose is destined to be a nutritive element for the myocardium.

Adrenalin may be added to the infusion or given separately hypodermically; 15 to 20 drops of a 1 : 1000 solution is an excellent stimulant. Strophantine given intravenously is sometimes very effective. It is found on the market in sterile ampules, each containing 1 cc of a 1 : 1000 solution. This injection may be repeated six to ten hours after, but generally not again. Small but often-repeated doses of strychnine are also of good value. Alcohol seems to have but little effect. When the acute stage of shock is over, digalen, given hypodermically or intravenously, proves sometimes an excellent stimulant.

However, the best of all methods for the treatment of shock is *blood transfusion*; it may be done by the direct or indirect method. The indirect method, however, is the one which is within the reach of everyone on account of its simplicity, and what is more, it is just as effective as the method of direct transfusion. The indirect method which I have devised can hardly be improved in its simplicity.

**Crotti's Technic of Indirect Transfusion.**—Although thoroughly familiar with the technic of vascular surgery, I have always felt that the direct transfusion of blood by arteriovenous anastomosis is a very delicate operation and too often unsuccessful. Everyone who is familiar with that kind of work knows how difficult it is to anastomose properly the small vein of a child, for instance, with the large radial artery of a man, and even when the anastomosis has been successfully performed, there is no way of telling whether the arterial blood is running into the vein, and if it is, how much has been transfused. The operation is a long and difficult one. The same objections are true for the other methods of transfusion as, for instance, when performed with small glass tubes prepared with alboline or paraffin. Therefore I sought to find a simpler method which might be just as efficient, if not more, and become more popular on account of its simplicity. It is called *indirect transfusion of blood*.

With Dr. Shilling, pathologist at Grant Hospital, Columbus, Ohio, I made a series of experiments on dogs in order to determine the coagu-

lation time of the blood, when withdrawn, first, in a sterile dry glass; second, in a glass boiled in normal salt solution; third, in a glass boiled in alboline. The average coagulation time was from five to eight minutes for blood withdrawn in a sterile dry glass, and from seven to twelve minutes for blood withdrawn in glass boiled in salt solution or alboline. Therefore I thought there would be plenty of time to withdraw blood with a syringe from a vein and to reinject it into another one without running any danger of coagulation. This was indeed successfully demonstrated in each of our numerous experiments. We were able, provided that certain rules were followed, to withdraw several hundred centimeters of blood from the vein of a dog and to reinject it into the vein of another without a particle of trouble. I was able also to demonstrate the efficacy of the method in human surgery more than once.

**Technic.**—Iodine preparation of the skin of the donor. Local anesthesia with novocain, 1 per cent. Incision of the skin three or four centimeters long in the angle of the elbow. The cephalic vein is dissected out and cut at the upper end of the incision. The proximal end is ligated with catgut. To the distal end three small mosquito forceps are applied at an equal distance one from the other in order to maintain the lumen of the vein open. A small artery clamp applied a few centimeters below prevents the blood from leaking.

The same operation is performed on the recipient with the difference that the vein is ligated at the lower end of the incision.

A blunt needle which has been adapted to the syringe is introduced into the vein of the donor in the opposite direction to the blood current; blood is aspirated into the syringe, and reinjected into the vein of the recipient, in the same direction as the blood current.

The transfusion may be repeated as often as is necessary without coagulation, provided needle and syringe are freshly washed each time with a warm normal salt solution. The best plan is to have two needles and two syringes, and to have one set washed by the assistant while the other is in use. When transfusion is terminated the veins are ligated and the skin incision closed. By this method any amount of blood may be transfused from one patient to another, and the exact amount transfused is known. The fact that the blood is venous seems to be without importance. The technic is simplicity itself and may be used by anyone. A few bubbles of air are of no importance.

If one prefers to take arterial blood from the donor, he may do so by preparing the radial artery in the same way as described above.

**Postoperative Hyperthyroidism.**—Whoever has operated many thyrotoxic goiters must have occasionally met with this dreaded complication. Fortunately, postoperative hyperthyroidism is very much less frequent today than it was in the early period of thyroid surgery because

of our better knowledge, better technic, and better judgment, nevertheless this complication does occur, and sometimes very unexpectedly, no matter how small the surgical traumatism has been.

Generally speaking, we may say that postoperative hyperthyroidism is only an exaggeration of all the symptoms seen in Basedow's patients. It is characterized by palpitation, tachycardia, tremor, vomiting, fever, sweating, extreme agitation, hallucinations, psychosis, etc. Though often the operation is not yet terminated, the tachycardia is already intense, the pulse beating between 150 and 200. As soon as the patient comes out of the anesthetic he shows extreme agitation; jumps up in his bed; his whole body shaken by an intense tremor; perspiration is abundant, and although there is no mechanical obstruction in the trachea, the patient shows air hunger; temperature climbs up to 103 or 104° F. or more; the highest I have seen was 107° F. The patient becomes more and more restless, wants to get out of bed, and to go home; has hallucinations; sees people, and talks vehemently. The condition usually reaches its most acute stage toward the end of the second day. This peracute form of hyperthyroidism lasts one, two and three days and usually terminates in death. In the milder forms, however, the symptoms are less pronounced: the storm, less intense, is over sooner.

The nature of this postoperative hyperthyroidism is not yet clear. Rehn, Mikulicz, Moebius and others believe that it is due to an abundant resorption of thyroid secretions intensely toxic. This may be true in certain number of cases but this explanation does not hold good for all cases since Curtis and Delore have observed it after sympathectomy, Pollosson after a gynecological operation in a Basedow patient, and Crile, after only "the prick of a hypodermic needle." Since it appears after simple ligation, after enucleation or resection, no matter whether one leaves a raw surface or not, it would appear that the "raw surface" and "squeezed juice" hypotheses do not adequately explain postoperative hyperthyroidism. Kocher and Riedel believe that hyperthyroidism is due to general anesthesia. This, however, is not always true since it has been observed after the use of local anesthesia.

It cannot be denied, however, that the anesthetic, no matter whether ether or nitrous oxide is employed, is *per se* a potent contributing factor in the production of postoperative hyperthyroidism. Local anesthesia is far less liable to cause postoperative hyperthyroidism than general anesthesia.

Crile claims that postoperative hyperthyroidism is due to shock. Some authors think that postoperative hyperthyroidism is related to thymic hyperplasia. Most likely this is partly true since the thymus belongs to the chain of organs of internal secretion and with them that gland plays, as we shall soon see, a part in the production of postopera-

tive hyperthyroidism. At any rate, one thing in my practice seems to corroborate these views: Since, as routine work, I combine thyroidectomy with thymectomy, postoperative hyperthyroidism is far less frequent in my experience than it used to be.

In my judgment postoperative hyperthyroidism is nothing more nor less than a fulminating spell of the ordinary hyperthyroidism which we see every day in thyrotoxic patients. The symptoms are the same. The only difference is a matter of degree. In postoperative hyperthyroidism all the symptoms are greatly intensified sometimes to such an extent that the organism, unable to stand the impact, is swept away in two or three days by this tremendous wave of hyperthyroidism. Just as in an ordinary case of thyrotoxicosis, shock, be it psychic or traumatic, be it light or severe, is liable to determine a very acute spell of hyperthyroidism, so in any surgical intervention, be it ligation, resection, gynecological operation, or only the pricking of a needle as in Crile's case, the traumatic shock from the operation, the psychic shock from going through the ordeal, and the toxic shock from the use of the anesthetic, etc., are all factors which, with others, intervene in producing the thyrotoxic explosion called postoperative hyperthyroidism. It is consequently logical to consider postoperative hyperthyroidism and ordinary hyperthyroidism as having the same cause. As we have considered the latter, a *thyroneuropolyglandular disease*, so we consider the former as a *fulminating thyroneuropolyglandular spell*. The organism is suddenly flooded with an enormous amount of thyroid products, be it from overfunction of the gland or from absorption from the "raw surface" itself. The nervous system is running wild, either because driven by the toxic thyroid products or, because it has lost its "gyrostatic control," if I may say so. The polyglandular system is working at random, thus mobilizing toxic products of metabolism which only further aggravate the situation. In short, the entire thyroneuropolyglandular machinery is out of gear.

**Acidosis.**—Although of recent acquisition, acidosis is nevertheless of vast clinical importance. For years I have been impressed with the frequency with which the "acetone breath" was encountered in many of my postoperative cases. I thought for a long time that I had to deal with some transitory diabetes, but repeated examinations, however, failed to show the presence of sugar in the urine. In 1913 an article on the subject by two French authors, Chavain and Oeconomos, enlightened me considerably, as they showed that the symptoms which I had observed were due to acidosis. Since then other authors, among them Crile, have but confirmed their views.

Alkalinity is essential to life not only for animals, but for plants also. We all know that an acid soil remains non-productive until it



has been alkalized with alkaline fertilizers, that plants cannot grow in acidulated waters, and that if the alkalinity of the blood in animals becomes lowered, life ceases. All the fluids of the body except the urine and gastric juices are alkaline.

Acid is constantly being formed in the body as the result of many metabolic processes. Exercise, emotion, etc., increase the amount of acid in the blood which in turn activates the respiratory centers.

One of the most characteristic symptoms of acid poisoning is an "acetone breath"; furthermore, the tongue is coated or perhaps abnormally red, the face is pale, or sometimes flushed, the surface of the body is often cold and moist, nausea or vomiting may be present. The patient is exceedingly thirsty, and shows excessive nervous irritability. Acetone and diacetic acid are present in quantities more or less great in the urine.

It is a known fact that starvation is a great source of acidosis and that in a surgical case, the length of the pre- and postoperative starvation periods, the amount of anesthetic, and the amount of surgical traumatism, will be the deciding factors in the intensity of acidosis.

From the foregoing facts it follows that we ought to be able to prevent, to a certain extent at least, acidosis by reducing the pre- and postoperative periods of starvation to a minimum and by reducing the amount of anesthetic. That is what I have been doing as a general principle in my surgical work, be it goiter or any other form of surgery. I do not deplete the patient any more with cathartics: when a cathartic is deemed necessary it is given several days before the operation. Nor do I restrict the diet of my patients in the least unless there should be a special contraindication for it; on the contrary, I want them to eat plenty of food; even their last meal before operation must be a good substantial meal, rich in carbohydrates. In severe cases where I fear the operation will precipitate an impending acidosis, I have my patients take some food, as oatmeal, etc., just an hour or two before the operation. As soon as the operation is over and as soon as they have recovered from the anesthetic, I want them to take plenty of water, because just as the acid soil needs water, so does the acid animal body. Even if they vomit, water is still given plentifully, at least for a time, as it is a very simple and efficient means to clean out the stomach.

It may seem excessive to compel patients who may be vomiting to swallow food, yet in severe cases a few hours after operation as soon as the stomach has sufficiently quieted down, a carbohydrate food, as gruel, potato soup, etc., is given to the patient, and as soon as possible feeding is pushed to the limit.

Glucose and bicarbonate of soda are used freely before and after the operation. A day or two before the operation the patient is given 150

grams of glucose in water flavored with peppermint, which renders the taste of the mixture agreeable. At the same time the patient is given 5 to 10 grams of bicarbonate of soda daily. As soon as the patient has come back from the operating room a proctoclysis, 20 to 25 drops a minute, is started. The following formula is used:

Sodium chloride . . . . .	6.0 grams
Calcium chloride . . . . .	1.0 "
Potassium chloride . . . . .	0.3 "
Bicarbonate of soda . . . . .	100.0 "
Glucose . . . . .	150.0 "
Alcohol . . . . .	20.0 "
Aq. dest. . . . .	1000.0 cc

If the acidosis should become threatening a pint or two of the following solution is given intravenously:

Sodium chloride . . . . .	8.0 grams
Calcium chloride (non-crystallized) . . . . .	0.2 "
(if crystallized) . . . . .	0.4 "
Potassium chloride . . . . .	0.2 "
Bicarbonate of soda . . . . .	0.2 "
Glucose . . . . .	1.0 "
Aq. dest. . . . .	1000.0 cc

At the same time bicarbonate of soda is given *larga manu*, that is, generously by every possible way.

**Postoperative Fever.**—Postoperative fever may be caused by infection, or may be entirely independent of it.

In the preaseptic era infection was one of the most feared complications. It occurred after enucleation or after resection, and too often terminated by mediastinitis, empyema, and pericarditis, and finally by death. But in these days with conscientious and intelligent asepsis, with careful protection of the field of operation from surrounding parts, with the Kocher screen, and with carefully selected and sterilized suture material, infection is very rare; in fact, it seldom occurs. For three years consecutively I have not had a single infection.

There is, however, another form of postoperative fever which is not due to infection. It occurs the same day of the operation and usually reaches its maximum on the second or third day after operation. It oscillates between 102° and 103°, and seldom goes above 104° F. Exceptionally, however, it may go higher; the highest temperature I have seen was 107° F., which terminated by death. In ordinary conditions this temperature lasts three, four and five days and then gradually disappears. It is accompanied by an increased pulse-rate, and by

more or less marked symptoms of hyperthyroidism. This postoperative fever occurs both in simple and thyrotoxic goiter, but it is far more frequent and far more marked in the latter condition.

The pathogeny of the postoperative fever is the same as that of postoperative hyperthyroidism.

**Postoperative Tetany.**—Tetany was very frequent at the time when total thyroidectomies were performed and when the technic of goiter operations had not reached the state of development which it has today. Nowadays postoperative tetany is rare. Kocher saw it only 5 times in his last 1000 operations; Mayo, in 1200 operations, saw it once; Frazier, reporting the results of 2000 operations done by American surgeons, found 8 cases of tetany reported, 3 of them being fatal; Boese in 410 cases, operated on by Hochenegg, found 2 cases of tetany. I have seen it twice in my surgical practice. Thyroidectomy does not need to be total in order to produce tetany. The removal of one lobe only is sometimes sufficient to cause it. The reason lies in the fact that, although only one or two parathyroids have been removed, the parathyroids of the other side are either insufficient or absent. Benjamins, who made a systematic examination of goiters removed by operation, found that in many instances one or two, or even three parathyroids had been removed with the goiter. Another reason why tetany may appear sometimes after partial thyroidectomy is that, on account of abnormal vascular development, the small artery which supplies the little parathyroid glandules is destroyed, causing necrosis of the parathyroids, and hence the tetany. Erdheim made thorough seriated microscopic examinations of the cervical region in 3 cases which died of tetany. In the first case he found no trace of parathyroids, but found two very small accessory parathyroids imbedded in the thymus; in the second case only one parathyroid was found but it was entirely necrotic; in the third case no trace of parathyroid tissue could be found. (See chapter on Parathyroids.)

**Symptoms.**—The symptoms of postoperative tetany usually appear in the next twenty-four hours after operation and are characterized at first by a pricking sensation and by a slight stiffness of the fingers. The symptoms usually reach their maximum on the third day and are always bilateral. Exceptionally, tetany may occur only six, eight, ten or fifteen days after the operation. Some claim that it may even happen months or years after. In the latter cases the operation cannot be held directly responsible.

When fully developed the disease is characterized by tonic and intermittent spasmodic contractions in the flexor muscles of the upper extremities. Such contractions are present, too, but in a lesser degree in the lower extremities. The interval between the contractions is at first

quite marked, but gradually they become more intense and more frequent. In severe cases the tonic contractions may last one or two hours; in such conditions the musculature of the back, the masseter muscles and the diaphragm may become involved. Of course all cases of tetany are not alike, and all do not show the same severity; some are of the mild type and show only "tetanoid" symptoms.

Besides the muscular contractions, four other cardinal symptoms are found in tetany. They are:

1. The *Chvostek symptom*.
2. The *Weiss symptom*.
3. The *Trousseau symptom*.
4. The *Erb symptom*.

The *Chvostek symptom* is a sudden and fugacious contraction of the muscles of the face obtained by a slight percussion on the facial nerve at its point of emergence in the parotid region. Percussion may be done with the percussion hammer or simply with the finger just as in the act of percussing the thorax. Percussion must be very gentle and soft.

Frankl-Hochwart distinguished three different degrees of the Chvostek symptom:

Chvostek I.—The entire facial musculature of the side percussed responds to a slight percussion made upon the facial nerve at its point of emergence in the parotid region.

Chvostek II.—Contractions are localized only in the ala nasi.

Chvostek III.—Contractions are seen only at the angle of the mouth.

The Chvostek symptom has been considered for a long time as pathognomonic of tetany, but it occurs also in conditions which are entirely foreign to parathyroid insufficiency. For instance, the Chvostek III may be found in tuberculosis, epilepsy, neurasthenia, and even in normal individuals. In interpreting the Chvostek III one should be sure that it is not of muscular origin, because sometimes percussion in the outer edge of the orbicularis oris may determine some fibrillar contraction in that muscle, which thus becomes a source of error of interpretation. On the other hand, the Chvostek may be missing in very marked cases of true tetany. It is more often present in stomach tetany of adults than in infantile tetany.

The *Weiss symptom* is a sudden contraction of the muscles frontalis corrugator supercili and orbicularis oculi, taking place when the temporal and zygomatic branches of the facial nerve are percussed at the outer angle of the orbita.

The Chvostek and Weiss symptoms are caused by an exaggerated excitability of the facial nerve, often causing the entire facial musculature to assume a peculiar expression known as the "tetanic face." In this



condition the angles of the mouth are drawn; the nasolabial groove is more deeply marked, and there is an anxious expression over the forehead with the eyelids remaining wide open.

*The Trousseau Symptom.*—In 1864, Trousseau saw that by exerting a circular compression on the upper arm of patients with parathyroid insufficiency, so as to compress the nerves and bloodvessels in the bicipital groove, spasmodic contractions and flexion of the forearm and wrist took place. At the same time the hand and the fingers took a position known since as the *accoucheur's hand*, or the *obstetrical hand* (Fig. 98). The best way to produce the Trousseau symptom is to exert circular compression on the arm with a rubber band. Often, however,



FIG. 98.—Tetany. "Accoucheur's" hand.

simple compression with the two hands in the region of the middle arm is sufficient. The Trousseau symptom may appear very quickly after circular compression has been started. In many other instances, however, compression has to be exerted for quite a long time before the symptom is obtained. In some cases the symptom appears only after compression has been removed.

Where the Trousseau symptom is fully developed and the accoucheur's hand is present, the fingers are found to be moderately flexed in their phalangometacarpal joints but extended in the remaining phalangophalangeal articulations. The thumb is in middle position between adduction and opposition and tightly closed against the fingers (Fig. 98); this compression may be so intense and may last so long that decubitus may take place at the point of contact of the thumb with the fingers.

The hand, as a rule, shows some degree of palmar flexion; it may be, however, moderately extended. The forearm is moderately flexed upon the arm and in the middle position between pronation and supination; at the same time it is adducted.

In the lower extremities the thighs and legs are extended; the feet show a plantar flexion of the toes and supination of the foot. The position taken by the foot is that of the "equine" or "varoequine" foot. Exceptionally, the foot may be pronated instead of supinated. The adductor muscles of the thigh being spasmodically contracted bring consequently the thigh into marked adduction. Lately, Schlesinger has described what he calls the "leg" symptom. The leg being fully extended on the thigh, if next the entire limb is flexed upon the pelvis, then, after two or three minutes, marked tetanic convulsions appear in the limb.

These spasmodic symptoms found in the upper and lower extremities, are known as the *carpopedal symptoms*.

The tendinous reflexes, as a rule, are normal. They may even be slightly diminished especially in the early stages. According to Falther and Kahn the patient after a severe tetanic spell complains of pain in the bones and in the joints.

Spasmodic cramps of the masseter muscles, of the tongue, of the diaphragm, of the bladder and rectum, are sometimes observed in severe cases. Spasmodic contractions of the esophagus and larynx may be present, too. Laryngospasm, however, is more frequently seen in infantile tetany than in that of postoperative. Bechterew, by compressing the phrenic nerve, caused at once a spasm of the diaphragm.

Intentional cramps are not so infrequently seen in postoperative tetany. They are characterized by spasmodic contractions in the musculature which for a few seconds may prevent the patient from performing the movements which he had intended to do; for instance, if shaking hands, the hand remains for a few seconds tightly closed, as if the patient had some difficulty in releasing his grip. Similar intentional spasmodic contractions occur in the lingual and esophageal musculature.

Frankl-Hochwart has shown experimentally that the Trousseau symptom is not due to the shutting off of the blood circulation in the arm, but is due to compression of the nervous trunks. After dissecting the nerves and vessels in the bicipital groove in dogs, this author was able to obtain the Trousseau symptom only when compressing the nervous trunks, and never when exerting a compression upon the arteries and veins alone. Pressure upon the nervous trunks of the thigh gives, too, the same symptoms which have been described above. According to Schlesinger, if compression is exerted upon purely motor nerves only, no Trousseau symptom occurs. It appears only in mixed nerves, namely, those containing motor and sensory fibers.

*The Erb Symptom.*—In 1878, Erb showed that in tetany the electric irritability of the motor nerves was gradually increased. This electric excitability is higher during the spasmodic contraction than during the intervals. This point is important to remember, especially in the latent forms of tetany where examination may show that during the intervals the Erb symptom is negative. As soon, however, as the Trousseau symptom has been elicited, the Erb symptom becomes positive.

The hyperexcitability of the nervous trunks is best determined with the galvanic current. It is characterized:

1. By musculature contractions on closure of the negative pole with currents of intensity, inferior to 1 milliampère when this current is applied on the ulnar or other motor nerves.

2. By muscular contractions at the opening of the positive pole with currents inferior to 5 milliampères.

3. By muscular contractions at the opening of the negative pole with currents inferior to 5 milliampères.

Symptoms of hyperesthesia are frequently found in connection with tetany and are especially localized in the upper extremities. They consist of a burning, pricking sensation, and dead feeling of the fingers. Sensory disturbances of the hearing, smelling, tasting apparatus are not so uncommon. The pricking and tingling sensations are sometimes intolerable.

The length of the convulsions may be very short or may last for hours. Sometimes there is only one spasmodic spell and then everything is over. Usually, however, the spells are numerous. As in tetanus, noise, touch, light, heat, cold, etc., may determine an acute spell. During convulsions, the muscles are hard, offer great resistance to passive movements and are spontaneously painful. Adrenalin and pilocarpin exaggerate the tetanic contractions and determine an intense vasoconstriction of the entire body, but especially of the face, hence the reason why patients with tetany look pale, although their blood is normal.

Just before and during the tetanic cramps there is tachycardia. The heart action is stronger, the sounds are more strongly marked, especially the second pulmonary and aortic sounds. Respiration is increased, too. Cyanosis and dyspnea may be present. The respiratory disturbances are partly due to spasmodic convulsions of the diaphragm, and partly to disturbances in the respiratory centers. As a rule temperature does not go very high. In some cases, however, it may be very marked. Even vomiting and diarrhea may be present.

Tetany should not be mistaken for tetanus, because in tetanus the tendinous reflexes are markedly increased, the heart is not involved, and the ordinary symptoms of tetany are not present.

**How Many Parathyroids May Be Removed before Tetany Appears?** This question cannot be fully answered. As a general principle, we should aim not to remove any parathyroid tissue at all. It is true that Erdheim found that one, two, or even three parathyroids had been removed in conjunction with thyroidectomy and that no, or very little, disturbance was observed. This would consequently tend to prove that one parathyroid alone is sufficient to prevent tetany. It would be dangerous, however, to bank too much upon that fact since we know that not only the number, but also the size of the parathyroids are two important factors in the production or non-production of parathyroid insufficiency. The volume of a single parathyroid might be larger than that of three other glandules taken together, while in other cases two small parathyroids, for example, may prove insufficient to protect the patient against parathyroid insufficiency. Consequently the aim of the surgeon should be to protect these little glandules and to safeguard them from any injury.

Despite, however, profound anatomical knowledge and good technic, postoperative tetany will sometimes occur. I have observed a case of tetany in a young girl whom I operated for a nodular colloid goiter, the size of a small egg, located in the isthmus. This median goiter was simply enucleated. Both lobes were left untouched inasmuch as they were normal. No ligation of the thyroid vessels was undertaken, so that I cannot see how I might have injured the parathyroids, yet the day following the operation the patient developed a mild case of tetany which happily was cured in five or six days with parathyroid opotherapy and lactate of calcium. Tetany in this case does not necessarily mean that the parathyroids were injured, although it is still within the range of possibilities that on account of some abnormal anatomical condition a slight injury to their nervous and blood supply might have occurred, thus putting them in a state of temporary insufficiency. It is more probable, however, that for some reason or another, they had been temporarily inhibited in their function. Some parathyroids, like some other organs, may normally have a reduced functional capacity; they may be congenitally weak, too. In ordinary conditions, however, they are still able to meet the physiological requirements of the metabolism, since their insufficiency is only potential. But let them be confronted with some abnormal condition, then they at once become insufficient to their task.

**Prognosis.**—The prognosis of postoperative tetany depends upon the quantity of parathyroid tissue left. The more removed, the worse the prognosis. In the first case reported by Erdheim, where no parathyroid tissue was found, death occurred three days after accidental parathyroidectomy. In the second case, where the one parathyroid found was necrotic, and in the third case, where two tiny parathyroids were found imbedded in the thymus, death occurred seventeen days after.



Most probably, in the two latter cases, death was delayed on account of some partial function of the parathyroids present. If the two accessory parathyroids found in the thymus had been large enough and could have undergone a sufficient compensatory hypertrophy, death very likely would not have taken place. Most likely, some of the cases of chronic tetany which we sometimes observe can be explained in the same way: the normal parathyroids, for some reason or another, having ceased to functionate more or less entirely, the accessory parathyroids partially supply their function but are not capable, however, of offsetting the loss of the main parathyroids.

The course of tetany in experimental pathology is the same as the one seen in human beings. The disease may become extremely acute or may take a very chronic, slow course. Exacerbations without any apparent cause are apt to be observed. In animals tetany differs materially with the species of animal involved. For instance, dogs develop a markedly acute and rapidly fatal tetany after complete thyroidectomy, while monkeys show a more chronic form of the disease. In human beings, too, we observe a great variety in the form and intensity of tetany. From the most severe forms, which are rapidly fatal, to the lightest form of the disease, all stages can be found. Postoperative tetany, no matter if severe or light, must always be considered as a serious complication, since we know that even the lightest form of tetany will, for no apparent reason, suddenly show marked exacerbations which may terminate in death. Von Eiselsberg seems to think that when tetany occurs late, that is, after a certain period of time after operation, its prognosis is more serious than in cases of tetany occurring at an earlier period.

Postoperative tetany may retrocede spontaneously in about 35 per cent of the cases. When death takes place it is caused by spasm of the glottis, of the diaphragm, or of the bronchi. Postoperative tetany has a great tendency to become chronic. When such is the case it becomes a troublesome disease since it is hard to manage by therapeutic treatment.

**Treatment of Tetany.**—*Opothrapy with fresh parathyroids* taken from cattle or horses has proved effective in a great many instances. Parathyroids may be given, too, in dry form either in powder or tablets. The results, no matter whether the parathyroids are taken in fresh or dried states, have not always been satisfactory. At any rate, large doses of parathyroids must be given in order to obtain good results.

Having observed that in tetany, elimination of calcium is enormously increased, and that the treatment of such animals with calcium, strontium and magnesium diminishes the excitability of the motor nerves to such an extent that the spasmodic contractions disappear, MacCallum and Voegtlin thought that tetany was due to a poisonous

substance circulating in the blood and depriving the tissues of their calcium content. They consequently advocated the use of calcium in treating parathyroid insufficiency, the results of which have been very satisfactory. Other authors, as Parhon, Urechi, Berkeley, Beebe, Bell, Martin, Biedl, have confirmed these findings and results. They claim that calcium, strontium and magnesium act directly upon the nervous trunks and render them incapable of transmitting the noxious impulses causing the tetanic convulsions. Musser was able to check tetany in twenty-four hours after administering calcium lactate to one of his cases. Halsted, while treating a chronic case of postoperative tetany, replaced the parathyroid opotherapy by lactate of calcium and obtained excellent results.

In 1914, Bergeim, Steward and Hawk found that after thyro- and parathyroidectomy, there was a slight retention of calcium. The urinary calcium secretion was low, averaging 0.0134 gm. per day on a daily injection averaging 1.6736 gm. of calcium oxide. A slight increase was observed during the period of study of the calcium content of the blood. No symptoms of tetany were noted in a case which survived operation thirty-nine days. The low urinary and blood calcium values were considered as showing deficient absorption of calcium. He explained the non-occurrence of tetany as due to the high calcium intake and to the development of the compensatory mechanism in which the pituitary body may take part.

Arthur and Schaefermann, on the other hand, did not obtain good results with calcium treatment.

Calcium is best used under the form of lactate. *Lactate of calcium* is given by mouth or rectum in a 10 per cent solution, 4 grams every three hours, or subcutaneously in a 5 per cent solution. The only inconvenience connected with this medication is that it must be given in increasingly large doses. Furthermore, the cure is not permanent but lasts only as long as the medicament is used. If the patient still possesses some parathyroid tissue, calcium lactate may tide the patient over the danger period until the parathyroid tissue has undergone compensatory hypertrophy.

Hot-packs, too, are a good therapeutic measure in the treatment of tetany.

**Grafting of the Parathyroids.**—Two different conditions may occur.

1. During operation a parathyroid may be inadvertently removed. In that case there must be no hesitancy as to what should be done. This parathyroid must be reimplanted at once in the thyroid tissue which is to be left *in situ*, as shown by Halsted. The thyroid is selected on account of its rich vascular supply. The chances for success for this autotransplantation are very good. We know that experimentally it

has been shown time and time again that autotransplantation could be made successfully. Christiani, for instance, showed that transplanted parathyroids could be still physiologically active five years after transplantation.

2. We may have to deal with a patient who, during operation, has been deprived of one or more parathyroids, and in whom a marked parathyroid insufficiency sometimes occurs later. In such cases, of course, autotransplantation is out of the question. We must resort to *heterotransplantation*. We know experimentally that in the majority of these cases this method has proved to be a failure. Its effects, as a rule, are only temporary and last only during the time necessary for the grafting to become absorbed. Consequently, if one wishes to resort to this method he must be sure that there exists a parental relationship as close as possible between the donor and the recipient. The ideal would be to obtain a parathyroid from someone closely related to the patient, as father, mother, or sister. Not only such close parental or family relation is of importance, but the age, sex and the conditions of the life of the donor and recipient should be approximately alike, since it is easily understood why a parathyroid removed from an old man and transplanted into a young child will have less chance to be successful than if the donor were also a child. If all these requirements are met, the grafting may then become permanent. Such an operation becomes, more strictly speaking, a *homoiotransplantation*.

In order to be successful the homoiotransplantation must take place in an individual in whom parathyroid insufficiency is well defined; if that is not the case the grafting will not "take." This fact has been demonstrated experimentally by Halsted, Christiani, and others. On the other hand, Iselin has shown that if parathyroid insufficiency is very marked, the chances for the grafting to "take" are greatly diminished. All this shows that the conditions of nutrition must be of a certain kind to allow the grafting to become successful. In such cases it is better to submit the individual to be grafted to a previous treatment with lactate of calcium or to parathyroid opotherapy.

The results of grafting should not be expected to become noticeable before six to ten weeks.

*Have we the right to parathyroidectomize an individual, even partially, in order to benefit another?* The importance of the parathyroids is too vital to deliberately remove one or two parathyroids from one patient in order to benefit another. I do not think a surgeon should do so even with the consent of the donor, for who knows whether the parathyroid tissue left will be sufficient to meet not only the physiological purposes, but also the increased demands made upon the system, when pathological conditions occur, as infectious diseases, etc.? A woman who is liable

to become pregnant should never be deprived knowingly of one or more of her parathyroids, because eclampsia seems to be too closely associated with parathyroid insufficiency. At any rate, if one wants to transplant a parathyroid from one individual to another, it should be done only after having ascertained by dissection that the others are seemingly normal. Everyone who has had some experience with the dissecting of that region knows how difficult it is sometimes to find the parathyroids. At any rate, it would mean a long, tedious work which might endanger the life of the very organs one is taking so much trouble to save. Homoiotransplantation should, consequently, not be undertaken unless for some especially strong motives.

The only possibility which then remains is to take, as Kocher did, the parathyroids from someone who has just died by suicide, or as Pool did, from someone who had died from a disease which would not prove to be detrimental to the recipient. The shortest possible time should be allowed to elapse between the removal and the transplantation. The best thing to do is to dissect the parathyroids as soon as possible after death of the donor and to put them in a warm Locke solution, or better, in the blood serum of the recipient himself while he is being prepared. The method known as the *method en semis*, spoken of when dealing with transplantation of the thyroid, may be used here, especially if the parathyroids are of good size. One or more parathyroids may be used.

The place of choice for parathyroid transplantation is the same as for thyroid transplantation. It may be done either in the abdominal walls between the muscles and the peritoneum or in the tibia. The thyroid itself and the spleen should afford good chances for success. The same rules indicated for thyroid grafting apply for parathyroid transplantation. The operation should be done very rapidly; the glandule should be handled with greatest care and gentleness; hemostasis of the cavity where the grafting is done should be absolutely perfect, and no antiseptic whatsoever should be used for the instruments, the hands, etc.

**Pulmonary Complications.**—For a long time pneumonia and bronchopneumonia had been among the postoperative complications threatening most the life of the goiter patient. This was due partly to the fact that at that time large goiters with their complications were frequently seen and partly to the indiscriminate and ignorant use of the anesthetic. Nowadays the operations are done to patients whose general condition is better. We understand the use of the anesthetics better, and we are more skilful in administering them. Consequently pneumonia and bronchopneumonia are certainly much rarer complications than formerly. In over 2200 cases I have observed 5 cases of pneumonia, one of them following tracheotomy.



**Postoperative Dysphagia.**—After operation for simple or toxic goiter the patients often complain of dysphagia for twenty-four to forty-eight hours. This is likely due to the involvement of the esophagus in the aseptic inflammatory processes following the operation, and possibly to the injury of some of the pharyngo-esophageal plexuses, during the various manipulations occasioned by the removal of the goiter.

**Postoperative Hematoma.**—Despite the greatest care in ligating every bleeding vessel, and especially when no drainage has been used, a moderate postoperative hematoma is sometimes observed. It is an unpleasant but insignificant complication. This postoperative hematoma is better left alone. It often drains spontaneously ten to fifteen days after. If not, and if at that time the swelling is still marked, some of the blood may be aspirated with an aspirating syringe, cautiously in order to avoid a fresh hemorrhage *a vacuo*.

Far more serious, however, although rather rare, is the acute postoperative hematoma occurring usually a few hours after the operation. The patient may not yet have recovered from the anesthetic. His respiration becomes more and more labored; he is blue, cyanotic, his voice is husky. If the nurse in charge of the case is not keenly alive to the situation, the patient may suffocate before aid can be brought to him.

The only thing to do, is to cut open the bandage at once. An enormous swelling of the whole neck will then be observed. The opening of the wound is imperative and *at once*. This is done in the patient's bed. The clots are removed, the bleeding-point located and tied, and the wound sewed up again, layer by layer, as before. A small gauze bandage may be left in the wound for forty-eight hours. Usually no infection occurs and the cosmetic results are excellent.

This possible complication after thyroidectomy must be always borne in mind. Therefore, it is wise always to have a tray with all the necessary instruments, suture material, adequate light, etc., ready for an emergency. It is best to have the tray in the patient's room, or nearby.

**Raising of the Scar.**—In spite of the greatest care on the part of the surgeon, some patients will sometimes "raise" a scar and form large, thick, unsightly elevations resembling cheloids. In some cases the surgeon is really not to blame for this, since it is a pathological peculiarity of the patient. In the majority of cases the raising of the scar, however, is due to a "beveled" incision. Hence the necessity for using a fine, sharp knife and of holding it perpendicular to the skin while cutting.

**After-treatment.**—I cannot do better than to quote the entire section of Ochsner's paper bearing on this subject:

"By far the most important point in the surgical consideration of this condition consists in the after-treatment, because with careful after-treatment almost all of these patients may become nearly as use-

ful as they were before they began to suffer from exophthalmic goiter, while in cases in which the after-treatment is not carefully carried out, practically all of these patients develop a condition as bad, if not worse, than that with which they presented themselves primarily for surgical treatment. The surgeon should bear in mind, in the first place, that practically all of these patients belong to a class of neurotics, and that this undoubtedly had much to do with the development of their goiters primarily, and that unless this condition is carefully taken into consideration in the after-treatment, the weakened physical condition of the patient will not be able to bear the wear and tear to which the neurotic tendencies would surely expose the patient. The same is true concerning the diet which is habitually chosen by the patients, which is usually exceedingly unwholesome, and it is consequently important that they be impressed with the fact that unless they adhere to the use of a reasonable diet, their chances for permanent recovery will be slight. We have always given these patients printed directions which contain all the important rules to be observed, and we have advised the patients to read these directions at regular intervals and to follow them for many years. The following is a copy of the directions which we use in these cases, and which have proved eminently satisfactory. The patient received a mild tonic and a laxative and an absolute diet list upon leaving the hospital.

**Rules for Goiter Patients.**—1. You should avoid all excitement or irritation, like attending receptions, shopping, church-work, and politics.

2. You should get an abundance of rest by going to bed early and taking a nap after luncheon.

3. You should have an abundance of fresh air at night, consequently you should sleep with wide-open windows or on a sleeping porch.

4. You should eat and drink nothing that irritates the nervous system, like tea, coffee, or alcohol. Of course, you should not use tobacco in any way.

5. You should eat very little meat. If you are fond of meat take a little mutton, beef, or breast of chicken, or fresh fish once or twice a week, or at most, three times a week.

6. You should drink a great deal of milk, or eat things that are prepared with milk, such as milk soup, milk toast, etc.; cream and buttermilk are also especially good for you.

7. You should avoid beef soup or beef tea or any kind of meat broths.

8. You should eat an abundance of cooked fruits and cooked vegetables or very ripe raw fruits, or drink fruit juices prepared from ripe fruits.

9. You may eat eggs, bread and butter, toast, rice, cereals.

10. You should drink an abundance of good drinking-water, or if this is not available, you should boil your drinking-water for a few minutes, or drink distilled water."

## CHAPTER LI.

### THE THYMUS GLAND.

**Synonyms.**—Latin, *lactes*, on account of its milky appearance; English, *sweetbread*; French, *riz-de-veau*; Spanish, *el timo*; South German, *Bries*, *Briesel*, or *Brösel*; North German, *Kalbsmilch*; Italian, *il timo*.

**Etymology and History.**—According to Riolan, the word thymus comes from the Greek word *θύμος*, which means thyme and was used to designate the thymus gland on account of some resemblance in the shape of the gland to the leaves of that plant. Because of the intimate anatomical relation of this gland with the heart, Galen regarded the thymus as the “center of courage and affection.” Consequently, it may be possible that this great scientist derived the word thymus from the Greek *θύμος*, meaning courage. This explanation is that much more probable since the word *θύμος* also means heart.

There is nothing in the writings of Hippocrates to show that he was aware of the existence of the thymus gland. The first mention of the gland in literature was made by Galen, Rufus and Polydeukes. Their descriptions were based mostly upon dissections of animals for butchery and holocausts, and it was only in the seventeenth century that anatomists began to pay attention to the thymus. Vesalius, in 1650, and Bartholinus, in 1673, were the first to give pictures and descriptions of the gland. Vesalius thought its main function was to act as a cushion to protect the intrathoracic organs. In 1659, Wharton called attention to the resemblance of the thymus to the pancreas. In 1671, Regner de Graaf, von Lossius, Welsch, and in 1673, Thomas Bartholinus, described what, for the following two hundred years, was known as the central cavity of the thymus. In 1736, Ruysch ascribed to the thymus an excretory canal emptying into one of the large thoracic veins. The existence of this canal, however, was not admitted by his contemporaries Bassius, Cowper, and Haller, who considered the thymus as a lymphoid gland. Other authors described an excretory canal emptying into the esophagus, trachea, pericardium and the pleural cavity. An empty vein must have been taken for the excretory canal described by Ruysch and others.

From the 17th to the 19th centuries, almost every anatomist admitted the existence of central cavities in the thymus. According to their descriptions these cavities were in some instances so large that one could put the thumb into them. It is not necessary to say that these cavities

were purely artefacts. Curiously, the division of the thymic parenchyma into the cortical and medullary substances passed long unobserved, and it was only in 1812 that Lucae began to doubt the existence of these central cavities and to hint at a division of the gland into two distinct portions, the *cortical* and the *medullary* substances. During the first half of the 19th century there was still considerable speculation as to the existence of a central cavity, some leaning toward its presence and some denying it. Those opposed to the existence of the central cavity were Simon and Kölliker, while Gerlach, Hassal, Ecker, Leydig, et al., were for its presence.

During the 16th and 17th centuries, the thymus was considered a receptacle for the chyme, or a supplementary organ of the breast and as a producer of its milk secretion. This latter physiological conception must have been due to the erroneous anatomical description of thymic cysts filled with lymph secretion or fluids of milky appearance. Mistaking, with Hewson, Hassal's corpuscles for nerve bundles, Ehrenberg, in 1836, went so far as to consider the thymus gland as some distant diverticulum of the medulla oblongata.

Although during the 18th century, some authors voiced the opinion that the thymus should be regarded as a lymphoid organ, it was only from the middle of the 19th century that a polemic began to take place regarding its real nature; some contending that it was a lymphoid, others, that it was an epithelial organ like the thyroid, the adrenals, etc.

During the second half of the 19th century, the anatomy, histology and physiological involution of the thymus became much better known, due to the researches of Kölliker, Jeandrassik, Friedleben, Toldt, et al. Waldeyer dealt a death blow to much theory by claiming that the thymus disappears entirely during life. Mauer made very complete researches as to the embryological development of the thymus in vertebrates, and Beard, in selachians. Stöhr described the histology of the gland. Schaffer studied the histology of the gland in insectivora especially and in vertebrates in general. Maximow studied the histology of the gland in mammals, amphibians and selachians, but possibly the most important work of all was done by Hammar, as will be seen in the course of this treatise.

### COMPARATIVE ANATOMY.

In chordates, especially in *amphioxus*, the thymus has not yet been found with certainty. It is not positive that the small canals discovered in *amphioxus* by Boveri, in 1909, are of thymic origin. The same is true of cyclostomata. There, too, the presence of the thymus is still doubtful. Although failing in *myxnoïdes* and the *petromyzontes*, lymphoid tissue



resembling very much the thymic parenchyma has been found in *ammocetes*.

If the presence of the thymus in cyclostomata is doubtful, there is no longer any doubt about its existence in *gnathosomes*. The thymus in the selachians (trout) was described by Robin, in 1845, and Ecker, in 1847; their findings were confirmed by Stannius, Leydig, etc., and especially by Hammar. It constitutes a unique organ, well lobulated, divided into septa, and possessing a cortical as well as a medullary substance. No Hassal's corpuscles are present; it is subcutaneous and physiological involution occurs regularly.

Stannius and Leydig discovered the thymus in *teleostians*, and their findings were corroborated by Mauer, in 1886; by Schaffer and Hammar, in 1908. It is usually tri-lobated and possesses a cortical as well as a medullary substance. The presence of Hassal's corpuscles could not be confirmed by Hammar, although other authors claimed that they had found them. The thymus of teleostians undergoes physiological involution.

The thymus of amphibians is quite well designated and known. According to Leydig, Simon, Maurer, Druner and Stannius, the thymus in tritons, salamanders and frogs is very superficial, extending up to the symphysis menti. It is of a nodular surface, shows a tendency to lobulation, and takes its origin from the second branchial cleft. In amphibians involution takes place, more or less, late in life. Typical Hassal's corpuscles are seldom found.

The thymus in *reptiles*, such as lizards, snakes, etc., is bilateral and composed on each side of two lobes, one located anteriorly to the other. It is more or less whitish in color and the posterior lobe is longer than the anterior. Usually, the right lobe is larger than the left while the cortical, as well as the medullary substance, is distinct. In turtles the thymus was for a long time mistaken for the thyroid. In *emydosaurians* the thymus is unusually large. In the crocodile, for instance, it extends from the mandible to the pericardium.

In reptiles the tendency of the thymus to division into two lobes on each side is due to its embryological origin, inasmuch as it is formed by proliferation of the second and third branchial clefts. The absolute presence or absence of Hassal's corpuscles in the thymus of reptiles is not definitely settled. Involution takes place in rather old age.

The thymus of birds was described by Morgagni, in 1762, while Meckel, Hammar, Simon, Ecker and Pensa, have added much to what we already knew about the thymus of birds. It is located in the neck, is bilateral, and in most birds is lobulated. In chickens, in long-legged and marsh birds, the thymus extends far up to the middle of the neck, whereas, in singing, and birds of prey, it extends up to the lower jaw. At some

stages of life, it possesses a distinct and rather large lumen. Hassal's corpuscles are very uncommon and physiological involution does not seem to take place. Hammar called attention to the fact that the thymus in chickens is unusually large. According to Hammar and Soli, the thymus of birds originates from the third and fourth branchial clefts.

In mammals, Hammar states, the thymus may be divided into three types according to their positions:

1. The *cervical type*.
2. The *thoracic type*.
3. The *cervicothoracic type*.

In the hog, for instance, the thymus is mostly cervical, very little being found in the mediastinal space, while in mice it is entirely cervical, and the same is true for insectivora.

The *thoracic type* is the one found in man, the horse, the elephant, the monkey, etc. In carnivora, the thymus is mostly intrathoracic. In the dog, according to Ellenberger and Baum, only one-fifth or one-sixth of the organ is cervical. It is of endodermal origin due to proliferation of the third branchial cleft. At first, it is represented by two small canals, whose distal ends begin to proliferate. The budding of these thymic bundles finally culminates in the formation of the thymus gland. The upper portion of the thymus remains in intimate connection with the lower portion of the thyroid. During this process of growth it passes mostly in front of the left innominate vein until it reaches the pericardium, but in some instances it may pass behind the left innominate vein. In the third embryonic month the thymus fuses, so to speak, with the pericardium; then, according to Tourneux and Verdun, an atrophic process occurs in the upper part of the thymus, which finally reduces the upper pole to a mere bundle of connective tissue, still remaining, however, in relation with the thyroid.

The *cervicothoracic type* is best illustrated by the thymus found in sheep. It lies partly in the thorax and partly in the cervical region. We do not yet know with certainty if the cervical type is due to the thymus IV, or if it is a separated portion of the thymus III. The cervical portion, of course, varies in size and length, but it may be so long and large as to reach the base of the skull.

**Embryology.**—There is no doubt that in all vertebrates the thymus is an organ of branchial origin. However, the number of branchial clefts involved varies. In lower vertebrates, for instance, the thymus takes its origin from as many as five branchial clefts. It must be said, however, that this branchiomic origin of the thymus has been questioned by Hammar. In mammals, in a general way, we may say that the third branchial cleft is responsible for the thymus. If it is true that in man, sheep, rats, etc., the thymus takes its origin by proliferation

of the epithelium of the third branchial cleft, thus becoming entirely an *endodermal* organ, nevertheless in some of the mammals, the thymus is of *endo-ectodermal* origin; the so-called *sinus cervicalis* participating in the formation of the thymus, too, as for instance in hogs, guinea-pigs, etc. Besides the mixed type we find the genuine *ectodermal* thymus, as in the mole, where the epithelium of the sinus cervicalis alone is responsible for the thymus.

In the human embryo, proliferation of the third and fourth branchial clefts takes place almost simultaneously in their dorsal as well as in their ventral portions. The dorsal proliferation of these two clefts will give rise to the parathyroid III and IV; the ventral proliferation will give rise to the thymus III and IV. These proliferations are known as the parathyroid and the thymus "anlagen." The thymus "anlage" III undergoes elongation but remains for quite a long time in intimate connection with the parathyroid "anlage" III through a bundle of glandular tissue which is attached posteriorly to the sinus cervicalis. It remains, too, in very close contact with the thyroid gland. This close relation of the thymus to the parathyroids and the thyroid gland will explain the origin of the thymic nodules which are found, not only around the lower poles of the thyroid, but also in the midst of the parenchyma itself.

Gradually, however, the thymus and the parathyroid III "anlage" lost their connection. The thymopharyngeal duct which still connects the thymus "anlage" III with the pharynx atrophies so that finally the thymus "anlage" becomes entirely free, retaining only toward its proximal end the form of a thin, elongated bundle, while the distal end undergoes marked proliferation. The elongated and thin bundle will constitute the upper pole of the thymus, whereas, the lower portion of the thymus "anlage" will become the well-developed intrathoracic thymus gland. During this development the thymus remains in intimate connection with the aorta and the innominate artery and undergoes displacement as these two organs do. At first, in the embryo, the thymus does not lie in front of the pericardium, but behind it. It is consequently located in the posterior portion of the mediastinal space; it is only later that it comes to lie in the anterior portion of that space. In a later stage the cervical portion of the thymus becomes atrophied and finally is reduced to a mere bundle of connective tissue.

As the left innominate vein appears only in a later stage of development, the variations in position and relation of this vein to the thymus will thus be explained. Usually, the vein lies behind the thymus; sometimes, however, it is found in front of it. Such a case was reported by Falls in 1915.

When fully developed the thymus may be regarded as composed of two pyramids, the right and the left, the bases of which lie on the peri-

cardium and whose apices extend up to the cervical region. One of the most constant varieties in the form of the thymus is that with the exaggerated formation of the cervical portion. This enlargement may affect the right lobe, the left lobe, or both at the same time. The left, however, seems to be the more often involved. This cervical prolongation is not necessarily of parenchymatous origin, but is often formed of a band of connective tissue due to regression, and connective tissue degeneration of the cervical portion of the thymus; it contains bloodvessels and comes in intimate connection with the lower pole of the thyroid and constitutes what is known as the *thyrothymic* ligament.

Besides the formation of the thymus known as the *thymus III*, because of its origin from the third branchial cleft, there is also what is known as the *thymus IV*, or *parathymus*, taking its origin from the fourth branchial cleft. This thymus IV, or parathymus, never reaches any great stage of development; it gives rise to *accessory thymic nodules*. From the results of his study based on over 70 cat embryos, Stewart, in 1918, claimed that the ultimo-branchial body also contributes to the formation of the thymus IV.

**Accessory Thymus Nodules.**—Attention was called to the presence of accessory thymus nodules in the cervical region by Jeandrassik, Verdun and Kohn, in 1898. These thymic nodules may be divided into two groups: (1) those belonging to the thymus III; (2) those belonging to the thymus IV. The nodules belonging to the thymus III are due to specks of thymic tissue left behind by the gland during its descent into the thorax. They are usually found in the neighborhood of the cervical organs, especially the thyroid and the parathyroids. In my dissections of the cervical region I have more than once encountered such nodules and have ascertained microscopically that they were of thymic origin. These nodules are known, too, as *external thymic nodules*. According to Kohn, it is normal to find a small, external thymic nodule in the neighborhood of the parathyroids of the cat.

These accessory thymic nodules must not be confused with the so-called *internal thymic nodules*, which, as shown by Grosshuff in 1896, take their origin from the thymus IV. These nodules found in the thyroid and parathyroids, are embryological inclusions taking place at a time when connections between the parathyroids, thymus and thyroid are intimate. This fact is of very great surgical importance, since, if it were possible to remove the thymus entirely, there would still remain in the cervical region these thymic nodules III and IV which may offset the lost function of the thymus gland. Furthermore, in pathological conditions, as we shall see later, these nodules may acquire great importance. Intrathyroid nodules, according to Grosser and Betke, are more or less constant in young children up to two or three years of age. But



they are also frequently found in specimens of later life, provided one searching for them takes the trouble of making seriated slides. The knowledge of the existence of such accessory thymic nodules is important because it has been shown experimentally that after complete thymectomy these nodules undergo a compensatory hypertrophy. They may also play a part in the production of hyperthyroidism; finally, they may give rise to the development of tumors.

**Thymopharyngeal Fistulæ.**—In early embryonic life each lobe of the thymus has an excretory canal connecting the gland with the third branchial cleft. This is called the *thymopharyngeal duct*. This canal, however, undergoes atrophy in the beginning of the third month of embryonic life. Like the thyroglossus duct, the thymopharyngeal canal sometimes remains open, thus producing *cervical fistulæ* whose feature it is always to remain lateral, while the fistulæ developed from the thyroglossus duct are always median. Thymopharyngeal fistulæ begin on the lateral wall of the pharynx a little below the fossa tonsillaris; extend downward, passing above and in front of the hypoglossus nerve, then run between the carotids and reach the inner border of the sternocleidomastoid muscle, which they follow until they break through the skin, usually a little above the clavicle. In other instances the thymopharyngeal duct becomes partially obliterated, so that only portions of it retain their epithelial lining. These portions are then liable to give rise to cystic or solid tumors. The thymopharyngeal canal, like the thyroglossus duct, is lined with ciliated epithelium, which in some instances, however, may be of the squamous-cell type.

## HISTOLOGY AND HISTOGENESIS.

The thymus is formed by lobules varying in size from 4 to 11 mm.; ordinarily, they are of long, oval, or round shape, and they are usually separated one from the other by thin layers of connective tissue. Frequently, however, the separation is not complete; thin streaks of parenchyma bridge the distances between them.

The thymus is divided into two portions, the *cortical* and the *medullary*. The cortical, as well as the medullary substance, is composed of a reticulum or framework, or parenchyma, of blood and lymphatic vessels. As seen in studying embryology, the reticulum is of epithelial origin and in that respect differs from the reticulum found in the lymphoid tissues. In the medullary substance, it is formed by relatively large, inter-ramifying cells, thus circumscribing spaces containing cells of various natures. These reticular cells have a large protoplasm containing a nucleus from 6 to 8  $\mu$ . This nucleus is poor in chromatin. The reticular cells of the

cortical portion of the gland have a small protoplasm possessing long filamentous prolongations. The reticular cells of the thymus of the young as well as of the adult, and even of the senile, show mitoses, a fact which demonstrates that even in late life the proliferation of the organ is still taking place, thus strengthening Waldeyer's statement that the thymus is a functioning organ throughout life. It must be said, however, that proliferation is far more active in the earlier stages of life.

The separation between the parenchyma of the cortical and of the medullary substances is not a sharp one. This is due to the fact that the reticulum of the medullary substance only gradually loses its character to assume the one seen in the cortical substance. The cortical reticulum is very fine and very abundant.

The *cortical substance* is mostly composed of a large amount of small, dark cells with very little protoplasm, resembling histologically the genuine small lymphocytes, notwithstanding the fact that Stöhr claims that they are of epithelial origin. These cells are known as the *thymic lymphocytes*. The weight of evidence seems to show that the thymic lymphocytes are really lymphoid cells. The lymphocytes of the cortical substance vary in size, between large and small, while all intermediary sizes are also found. Most of the mitoses are found in the middle-sized ones.

The small thymic cells contain granulæ, which can be demonstrated by the Benda-mitochondria method, and in that respect, according to Pappenheimer in 1914, are identical with the lymphocytes of the blood. Pappenheimer furthermore claims that in plasma cultures there is a radical difference in the behavior of the small and large thymic cells. The former show practically no capacity for proliferation, but after a period of active motility undergo degeneration. The latter undergo an active growth often in the form of syncytial cells and masses. They are actively phagocytic toward the degenerating small thymic cells, thus establishing in Pappenheimer's judgment a characteristic histogenic difference between these cells.

Besides the thymic lymphocytes, *neutrophile* and *eosinophile leukocytes*, *plasma* and *mast cells* are present in the cortical substance. These cells seem to be the direct product of the karyokinetic division of the thymic lymphocytes. According to Sobotta, the mast cells seem to reach their full amount of basophile granulations only after they have left the thymic parenchyma and have reached the interlobular connective tissue. Like the plasma cells they do not show mitotic figures.

The eosinophiles are very abundant from the seventh month of embryonic life up to a few months after birth. They then diminish very rapidly in number during the first years of life and are mostly absent after the tenth or twelfth year.

The *medullary substance*, in a gross way, shows the same elements found in the cortical substance. Karyokinetic figures are found less often than in the cortical substance. Mono- and polynuclear leukocytes and eosinophiles are present, but plasma and mast cells are absent. The latter seem to be found only in the cortical substance. Lymphocytes are less numerous than in the cortical substance.

Beside the cellular elements thus mentioned the medullary substance contains *Hassal's corpuscles*, *irregular epithelial cords*, *myoid cells* and *giant cells*.

*Hassal's corpuscles* were discovered and first described by Hassal in 1846. Hammar, however, claimed that the real discoverer of these cells was Simon. They are already found in embryonic life and their appearance continues until physiological involution takes place. Some authors consider Hassal's corpuscles as vestiges of the epithelial anlage, or beginning, of the thymus. Beard thought they were the remains of the intrathymic parathyroids. Some authors regarded them as vestiges of the thymic ducts; others thought they took their origin from the endothelium of the bloodvessels, and finally others, as Hammar, claimed that they originated from the reticular cells of the medullary substance. After reading his description and after examining the histological pictures, one cannot help but be strongly impressed with Hammar's conclusion. Their size is quite variable, inasmuch as they measure from 10 to 300  $\mu$ . They are formed by concentric layers of large cells. The central portion of Hassal's corpuscles undergoes very quickly a degenerative process characterized by hyaline degeneration, and accompanied by a breaking up into small hyperchromatic particles of the central cells. At the same time many small particles due to fatty degeneration are found. Still, according to Hammar, the peripheric cells of Hassal's corpuscles always possess fine prolongations by which they remain in communication with the adjoining reticular cells.

Hammar described small, thin trails of epithelial elements which he calls "irregular cellular strings"; they seem to be usually in close connection with Hassal's corpuscles and the reticulum of the medullary substance. According to Hammar, they are very likely due to proliferation of the reticular cells, vary greatly in number, and seem to be more abundant in certain pathological conditions.

So far as the *myoid cells* are concerned, they have been found rarely in man and in mammals; once in a five-months' embryo by Pappenheimer and in dogs and cattle by Hammar, but they seem to be more or less constant in birds. These cells, too, are usually in close connection with Hassal's corpuscles. The myoid cells originate from the mesodermal cells, namely, the myoblasts, which in the early development of the thymus are frequently found around it. These myoblasts may become

intrathymic in an active or passive way, either by wandering into the parenchyma or by being drawn into it with the capillary vessels. These myoid cells are absolutely foreign to the thymus and consequently soon degenerate.

The *giant cells*, on the other hand, are frequently seen in the medullary substance of the human thymus. They seem to be spread more or less freely in the medullary substance, or seem to have at times an intimate connection with Hammar's "irregular cellular strings." On account of their syncytial-like aspect the giant cells may be considered as of reticular origin.

Finally, sometimes *ciliated epithelium* is found in the small cysts observed in the medullary substance. It is fair to assume that these cells are the remains of the epithelium of the thymopharyngeal duct which, we know, is often lined with ciliated epithelium.

*Is the thymus an epithelial or a lymphoid organ?* The statement made by Kölliker that the thymus was a typical epithelial organ during its embryological period of development, whereas, when once matured becomes a typical lymphoid one, attracted the attention, of course, of histologists and embryologists, but today opinions are still diverging. Some authorities claim that the thymi are due to the direct transformation of the epithelial cells into lymphoid tissue. This theory is known as the "*transformation theory*." On the other hand other authors claim that the thymic cells are invaded and replaced by mesodermal cells. This is the "*pseudomorphosis*" theory or the "*migration*" theory. According to the last-named theory, the thymus is a lymphatic organ whose parenchyma is formed by genuine lymphoid cells, which, however, are not at all embryonically so produced, but have migrated.

Maximow, Hammar, Johnson, Söderlund and Backmann, Ruben, Hanson, Zotterman, Hamilton, Helgesson, Ankarswaerd, Dantschkarow, Weill and Weidenreich are in favor of this theory. The defenders of the transformation theory may be divided into two groups: those who believe that a genuine transformation of epithelial cells into lymphoid cells takes place, as Kölliker, Beard, Maurer, Schultze, Tourneux and Hermann and Frenant; and those who consider the lymphoid cells as genuine epithelial cells, as Stöhr, Cheval, Marcus, Ganburzeff, Schridde and Fritsche. Stöhr, especially, claimed that the transformation of epithelial cells into lymphoid cells would contradict the law of specificity. In his opinion the thymus is, and remains, an epithelial organ, and although the thymic cells resemble the lymphoid tissue, they are nevertheless epithelial cells, which fact he believes can be demonstrated by using special staining processes. On the other hand, the researches of Hammar, Maximow, Weill and Weidenreich seem to convey the idea that the thymic cells are real lymphoid cells. Furthermore, Benckekoff, in 1916,



claimed that the thymic cells rise from wandering cells of mesenchymal nature that invade the epithelial "anlage" of the thymus. These small cells increase by their own mitotic proliferation and also at the expense of the large lymphoid hemocyto blasts, and finally differentiate into small lymphocytes. The "anlage" of the small lymphocytes is a stem-cell, polyvalent in nature, and capable of forming granular leukocytes as well as lymphocytes. Experimentally, Benckekoff claims that small lymphocytes can be changed into plasma cells and granular leukocytes, and furthermore believes that the latter blood cells descend directly or indirectly from polyvalent cells, which are of mesenchymal origin.

Badertscher thinks that the lymphocytes present in the thymus are all large lymphocytes which have migrated into it from the mesenchyme and that the small lymphocytes are formed by the repeated division of the large ones. The reticulum is of epithelial origin and so are Hassal's corpuscles.

On one point are the authorities more or less united, and that is in recognizing the epithelial origin of the reticulum of the thymus and of Hassal's corpuscles. Very few investigators, as Schaffer, Dustin and Salkind and Bell, consider Hassal's corpuscles and the reticulum as of connective tissue origin.

Some writers have tried to find a middle ground between the transformation and the migration theories, as for instance, Von Ebner, who claims that the medullary substance and Hassal's corpuscles are of epithelial origin, while the cortical substance is of lymphoid nature.

In order to show the disparity between the thymus and a lymphoid organ, Stöhr and Klose remark that the lymph node possesses a thick, connective tissue capsule, sending inwardly thick septa which form a strong meshwork. The capsule of the thymus, on the other hand, is thin; the septa exceedingly thin, and the thymic parenchyma is loosely adherent to the inner side of the capsule. Lymph nodes have a germinal center; the thymus has none. Schridde claims that the germinal centers spoken of in the thymus have been mistaken for bundles of the medullary substance, in which mitoses are not frequent, whereas, they are very common in the germinal centers. In the lymph nodes the proliferation of the cells takes place in the germinal centers; in the thymus it takes place in the cortical substance. The chemical composition of the lymph node is entirely different from that of the thymus, as shown by Ivor Bangs, in 1904. The amount of nucleinates, of albumin, of ash, is far greater in the thymus than in the lymph node, as shown by analysis:

	Thymus, per cent.	Lymph node. per cent.
Albumin . . . . .	15.52	13.79
Nucleinate . . . . .	3.15	.69
Ash . . . . .	1.59	1.05

Furthermore, in contradistinction to a lymph node the thymus in its prime possesses a tremendous regenerating power; after partial extirpation it is capable of regenerating and growing again almost to its previous size. No such phenomenon is observed in a genuine lymphoid organ.

Dustin, in 1916 and 1919, regarded the small thymic cells as the only fundamental, constant and specific element of the organ and that all other elements are inconstant and variable and only the result of metaplasia following degeneration of the elements. He concludes that the thymus is not a true gland but rather a center of nuclei metabolism acting as a reserve for the nucleins which are liberated by the hormones from other organs, such as the liver and pancreas. Dustin supports his conclusion by the work of Delazenne, who found that the thymus is among the organs very rich in zinc, thus being closely associated with the nucleolytic ferments.

Nothing has yet been said to prove conclusively that the thymus is a red-cell producing organ.

In conclusion, we may say that the thymus is an epithelial organ invaded by lymphocytes from the adjacent mesenchyma, and that these cells proliferate within the gland and come later to form the bulk of the thymic tissue. The epithelial component, however, persists as the reticulum and Hassal's corpuscles. The framework of the gland in the meshes of which lie the thickly crowded lymphocytes is formed by the reticular epithelial cells. Thus the thymus is a *lympho-epithelial* organ. The fact that we find in the thymus tumors of epithelial and connective tissue origin, carcinoma and sarcoma, will, I think, lend more strength to this conclusion.

**Involution of the Thymus.**—It was formerly thought that the thymus grew up to the second year after birth, and that it then gradually diminished and disappeared more or less entirely after the thirteenth year of life. Today, it is more generally accepted that the thymus is an organ belonging to the period of development. As soon as the physical development has reached its completion, the organism seems to have no more need of that organ, hence its atrophy. Consequently, we must expect to find the gland increasing in size and weight during the period of growth, and so it is. This condition seems to be true throughout the animal kingdom. This regression of the organ is known as its *physiological involution*.

In fish, in teleosts and in reptiles, the physiological involution of the thymus has been well demonstrated. The phenomenon is not so certain in amphibians. In birds, the physiological involution varies while in animals with powerful musculature, it takes place at an early period. In mammals it varies with the species; in cattle, for instance, it begins

from the fourth to the fifth year but is never completed. In the cat, it occurs from the second to the third year. In the horse involution takes place after the second or third year of life.

According to Ellenberger and Baum, in the newborn puppy the relation of the thymus to the body weight is 1:250; eight or ten days after, it is 1:170, thus showing an immense increase of the thymus in proportion to the body weight. After the second or third weeks, involution begins to take place, and progresses so rapidly that during the second or third months of life the relation of the thymus to the body weight is from 1:1200 to 1:1600. This regression takes place mostly in the intrathoracic portion of the thymus, and although it is true that the microscope is still able to reveal remains of the thymus in a ten-year-old dog, nevertheless the maximum of its development takes place about the fourteenth day after birth.

Physiological involution of the thymus in man was first described by Galen, who thought the gland reached its maximum weight and size at birth, and from that time on underwent atrophy. This view remained in force until Meckel's time. He thought the thymus increased in size during the first year of life; remained stationary for a few years and then disappeared about the tenth year. Later on, Friedleben, in 1858, asserted that the thymus increases in weight and size up to the second year, remains stationary from the fifteenth to the twenty-fifth year, namely, during the growing period, and then regresses until it finally disappears. Sappey, and especially Waldeyer, after very careful dissections of fresh cadavers, came to the conclusion that there is no such thing as total disappearance of the thymus even in old age. They found in cadavers of patients from sixty to eighty years old that there is always present in the mediastinal space a fatty mass of peculiar consistency and coloration, containing without any doubt remains of thymic parenchyma. Mitotic figures are also present, showing that the regenerating power of the parenchyma is still present. They consequently consider that the thymus function is never really suppressed during life and they furthermore claim, in accord with Hammar and Lampe, that the words, "persistence or reviviscence" of the thymus are misnomers. It is as erroneous to speak of the persistence or reviviscence of the thymus as if one were to speak of the persistence or reviviscence of the breast, kidney, or ovary. So, in conclusion, we may say that the thymus increases in weight up to the time of puberty, namely, between the tenth and fifteenth years; that during this time it reaches its maximum of development, and that it then begins to undergo a physiological involution but never disappears entirely during life. The following table will, I believe, prove the contention.

ABSOLUTE WEIGHT OF THE THYMUS DURING VARIOUS PERIODS OF LIFE.

Age.	V. Sury, grams.	Hammar, grams.	Schridde, grams.	Roneoni, grams.	Klose, grams.
Newborn . . . . .	14	13	13	10	9
1 to 5 years . . . . .	22	23	17	16	15
6 to 10 years . . . . .	29	26	20	21	18
11 to 15 years . . . . .	32	38	25	28	25
16 to 20 years . . . . .	..	26	20	20	20
21 to 25 years . . . . .	..	25	19	18	17
26 to 35 years . . . . .	..	20	14	14	14
36 to 45 years . . . . .	..	16	10	13	9
46 to 55 years . . . . .	..	13	7	9	6
56 to 65 years . . . . .	..	16	4	12	5
66 to 75 years . . . . .	..	6	3	5	4

WEIGHT AND MEASUREMENTS ACCORDING TO KASARINOFF-SCHKARIN.

Age.	Body weight in grams.	Weight of thymus in grams.	Length of thymus in centimeters.	Width of thymus in centimeters.	Thickness of thymus in centimeters.
Newborn . . . . .	3,190	11.7	7.9	7.9	1.7
1 year . . . . .	8,840	6.6	6.6	5.3	1.1
2 years . . . . .	12,270	8.1	8.0	3.0	1.6
3 years . . . . .	13,600	7.3	7.5	5.0	1.1
9 years . . . . .	19,000	11.0	8.0	6.0	1.5
10 years . . . . .	26,000	13.0	8.0	6.0	1.5
Adults . . . . .	....	8.2	5.9	5.6	1.5

These weights are by no means constant and invariable. Considerable variations may be found according to individuals, and anatomists do not all agree. However, these figures give a good idea of what the weight of the thymus may be expected to be at a given age in normal individuals.

E. R. Hoskins gives the following table:

Age, years, average.	Body weight, kilograms, average.	Thymus weight, grams, average.	Thymic paren- chyma weight, grams, average.	Thymus per cent paren- chyma, average.	Thymus per cent body weight, average.	Thymic paren- chyma per cent, body weight, average.	Lympho- cytes in blood, per cent, average.
Birth . . . . .	3.2	13.3	12.33	93.0	.0401	.0385	61.0 <sup>1</sup>
2.6 years . . . . .	14.2	23.0	19.26	84.2	.0162	.0136	55.5
9.0 years . . . . .	27.2	26.1	22.08	84.6	.0090	.0080	36.0
14.8 years . . . . .	45.5	37.5	25.18	67.1	.0041	.0020	23.0
23.3 . . . . .	67.0	24.7	4.95	20.0	.0037	.0007	23.0

<sup>1</sup> Percentage at one year, higher at birth. Leukocytes at birth equal 18,000 to 36,000 per cubic millimeter.



If these figures are correct, and if they have been taken from the study of a sufficient number of cadavers, this table would tend to show that, although it reaches its greatest size about the time of puberty, stripped of its fat and connective tissue, the thymus is comparatively much larger at the time of birth than at puberty. Furthermore, it shows that between fourteen to eighteen years of age the actual amount of thymus tissue decreases nearly one-half and the relative amount nearly two-thirds.

Besides the physiological involution just spoken of, there is another form of glandular regression occurring in connection with pathological processes of the body. Let us call this *pathological involution*. This form of involution has long been known to butchers since they noticed that animals worked to excess always have a small thymus, while animals not so hardworked have a larger one. Oxen driven under the yoke always have a smaller thymus than those not used for work. Söederlund and Backmann succeeded in reducing the thymus to one-tenth of its weight by submitting rabbits to a long fasting period. Hammar has shown that after three days of fasting the thymus of rabbits loses half its weight.

Physiological and pathological involutions show no difference in their mode of development. The regressive processes taking place involve mostly the parenchyma. At first the cells of the cortical substance become small and diminish in number, being drained off by the lymphatic vessels and veins. At the same time thin bands of connective tissue make their appearance. In a more advanced stage of involution the cortical cells become less and less numerous until finally the framework of connective tissue stands alone. During this involutional process, the gland shrinks from the periphery toward the center, so that finally it occupies the middle portion of the anterosuperior mediastinal space.

According to Hammar, involution may be divided into five stages:

1. The *infantile* stage, in which connective-tissue formation is only moderate and the parenchyma is still abundant.
2. The *juvenile* stage, in which the connective-tissue formation is far more abundant but in which the parenchyma remains about the same.
3. The *young adult* stage, when the connective tissue is still more abundant and the reduction of the parenchyma into the cortical substance is already quite marked.
4. The *adult* type, in which not only the connective-tissue formation is abundant, and the parenchyma much diminished, but fatty degeneration is also taking place.
5. The *senile* type, consisting mostly of connective tissue containing islands of parenchyma cells, the cells of the cortical substance having more or less entirely disappeared. However, for Hammar, mitotic figures are present in the thymic lymphocytes up to the sixtieth year of

life; furthermore, proliferation of Hassal's corpuscles is still taking place at that age, thus showing, what has been said before, namely, that the thymus is still a functioning organ.

The same involution takes place in pathological conditions, especially in acute diseases such as pneumonia, nephritis, etc. Usually the involution is a temporary one, and when the acute process is over the organ returns to its previous normal condition. In diseases of long standing, however, this is no longer true; there the thymus undergoes a sclerosis which remains permanent. Involution is then permanent.

### SURGICAL ANATOMY.

The thymus in human beings is mostly intrathoracic and is composed of two lobes, the right and the left. Usually, the two lobes can be easily separated; at least, that has been my experience in dissecting thymi in children. These two lobes come into intimate contact through their inner surface. As the thymus gland is composed of two independent lobes, it would be more correct to speak of the thymi instead of the thymus, as we say the lungs, the kidneys, the ovaries, etc. Speaking, however, in a generic sense, it is permissible to say the thymus instead of the thymi, as we say the ovary, the kidney, etc., as we do when speaking of these in a generic way. It is, furthermore, anatomically correct to say the right thymus, or the left thymus.

The form of the thymus is essentially variable and we may say there are no two thymi alike because the gland being soft, molds itself to suit its environments, filling up depressions between the tissues or molding itself upon the various resistant organs of the thorax, with which it comes in contact. It would be neither correct nor possible to describe the form of the thymus after its removal from the thoracic cavity, because, being soft, its form would be entirely destroyed. It is while in the cavity and while in relation with the thoracic organs that the form of the thymus should be considered. When such is done the thymus has more or less the shape of a pyramid with four surfaces, one anterior, one posterior, one internal and one external.

It is very common for authors to divide the thymus into a cervical and a thoracic portion. Although a true cervical portion is not uncommonly found, especially in children, it is by no means constant. When a cervical portion is present, it is usually in the early years of life, while the superior poles of the thymus have not yet undergone atrophy, or in pathological cases with thymic hyperplasia. In ordinary conditions, however, the cervical portion in adults is absent, or if at all present, is only very small. When at all present, the height of the thymic upper pole in the cervical region shows considerable variation. Sometimes,

PLATE XXXIII



Thymus of Newborn Baby (Natural Size).

Note that the thymus fills almost the entire mediastinum and extends upward as far as the thyroid gland. The figure illustrates very well what is called the "cervical" and the "intrathoracic" portions of the thymus. Note, too, the vessels extending from the thyroid to the thymus.





the two upper poles of the thymus come very near, or even in direct contact with, the lower pole of the thyroid; this, however, is not frequent, and it is more usual to find a space of one or two centimeters between

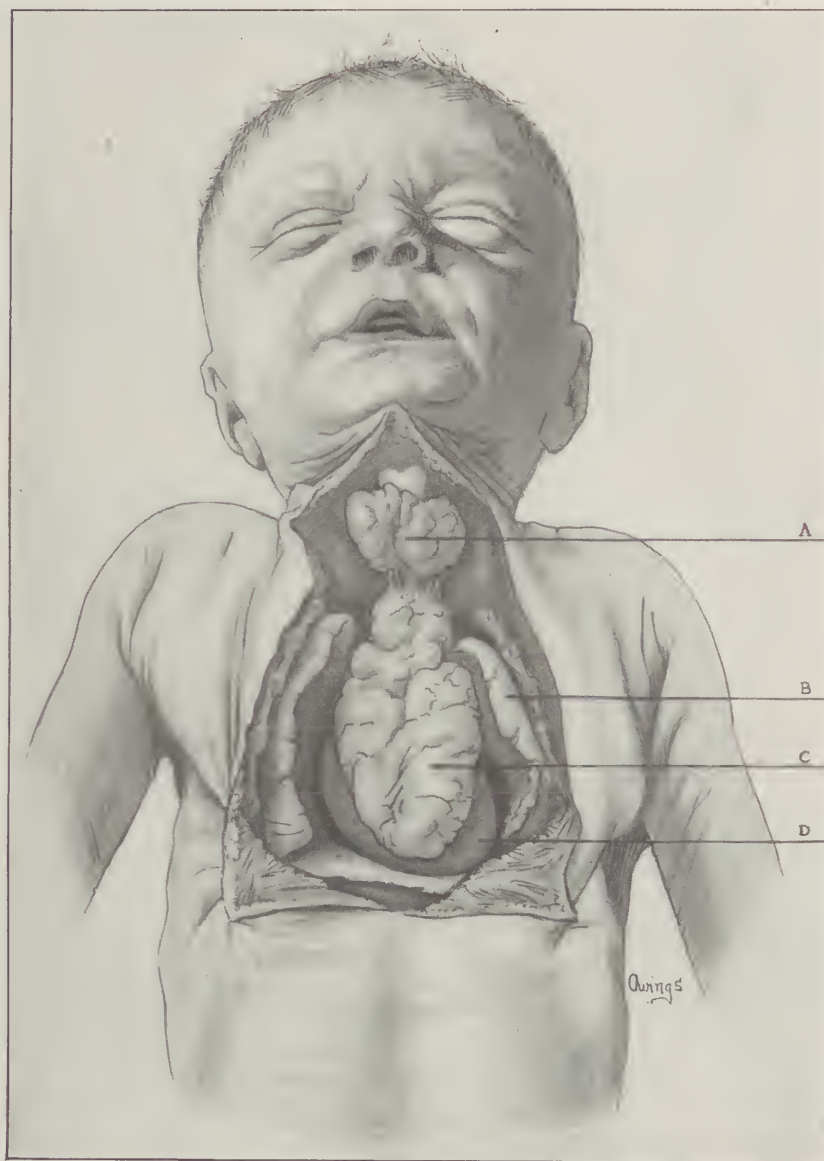


FIG. 99.—*A*, thyroid; *B*, lungs; *C*, thymus; *D*, heart.

the thyroid and the thymus. In cases of marked thymic hyperplasia, or if thymic nodules IV are present, the upper thymic poles may touch the lower thyroid poles. In rare cases the thymus has been found extending as high as the hyoid bone.

Which pole reaches the higher, the right or the left? There is no definite rule about this; the right upper pole being at times higher than the left, and *vice versa*. Most commonly, however, the two poles seem to be at the same height. In thymic hyperplasia accompanying thyrotoxicosis it has been my experience usually to find the left upper pole higher and larger than the right.

The upper poles of the thymus and the lower poles of the thyroid are always connected one with another by connective tissue ligaments containing branches of the inferior thyroid vessels. This ligament is known as the *thyrothymic ligament*.

The thymus has no isthmus. The two lobes are entirely separate, and if an isthmus between the two lobes has been described, it was solely due to a mistaken dissection. The fact that the two lobes come into intimate contact by the middle or lower portion of their internal surfaces might explain the error. The consistency of the thymus is soft. Its color is rosy in the fetal thymus, grayish white in the newborn, and of rather yellowish color in later life. It has a fine, lobulated surface, resembling in that respect the lobulation of the submaxillary glands.

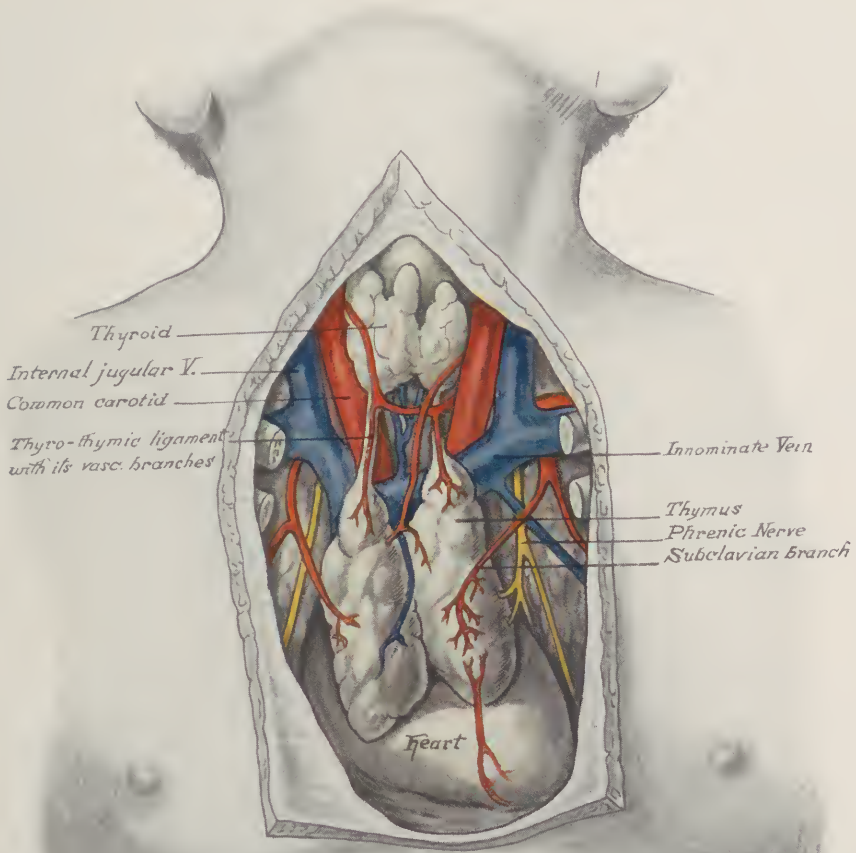
From the surgical point of view it is important to ascribe to the thymus two regions: the *cervical* and the *thoracic*. The cervical portion is the surgical region, whereas, the thoracic region is the non-surgical.

In the cervical region the thymus comes into contact in front with the sternothyroid and sternohyoid muscles; inwardly and posteriorly with the trachea and laterally with the common carotid. On the left side the thymus comes posteriorly in touch with the esophagus and the inferior laryngeal nerve.

In the thorax the thymus comes into contact anteriorly with the posterior surface of the manubrium and corpus sterni, down to the third or fourth intercostal cartilage. It is frequent, however, to find the thymus extending to the seventh or eighth intercostal cartilage. In the upper part of the mediastinal space the thymus is separated from the manubrium sterni by the origin of the sternothyroid and the sternohyoid muscles. The internal mammary arteries usually do not come into direct contact with the thymus, although once in a while dissections show that the distance between the two organs is a very slight one.

Posteriorly, the thymus lies upon the right auricle while a portion of the right ventricle covers the cross of the aorta, the pulmonary vein, and a portion of the superior vena cava. In some instances after pushing the vena cava aside, the thymus may come in touch with the esophagus and the bifurcation of the trachea. It is intimately attached to the left innominate vein and comes only in loose contact with the right innominate vein. On the left side the thymus is in intimate touch with the

PLATE XXXIV



Normal Anatomical Relations of the Thymus to the  
Other Organs.





vagus nerve and the inferior laryngeal. On the right side the connections are not so close. Furthermore, the gland lies upon the cardiac plexus.

Laterally, the mediastinal pleura comes into direct touch with the thymus; the same is true for the phrenic nerves, the right being more closely related than the left.

The thymus is surrounded by a capsule known as the *thymic capsule*. It is thin and in loose connection with the neighboring tissues. Inwardly, this capsule sends septa dividing the gland into lobes. These septa are very thin and easily breakable, a fact which is of great surgical importance when one wants to practice intracapsular thymectomy.

Although found "loosely connected" with the neighboring tissues, does not mean, however, that the thymic capsule is entirely free from adhesions with the neighboring organs. Just the opposite is true, as a few solidly fixed points are constantly found. The first fixed connection is in the upper pole. This connection takes place through the thyrothymic ligament. Another constant point of adherence of the thymus with another organ is at the pericardium. There, the pericardial sac is usually intimately connected with the posterior surface of the thymic capsule. Another point of contact exceedingly important is that of the thymus with the left innominate vein and the superior vena cava. Ordinarily, the connections, especially that of the left innominate vein with the thymus are close, although not intimate. It is usually easy to separate the veins from the thymic capsule. This, however, is not always constant and it is not uncommon to find cases where the adhesions are very strong, an anatomical point important to remember while practising thymectomy. Finally, another point of adherence much less important than those above mentioned is the one with the posterior surface of the manubrium sterni.

**Blood Supply.**—The thymic arteries are composed of a group of small, fine vessels taking their origin from the thyroid arteries, superior and inferior; from the internal mammary; from the innominate artery; from the intercostal arteries, and from the pericardiophrenic artery. The blood cells go through the medullary substance without giving off any ramifications, but when they reach the intermediate zone, the one between the medullary and the cortical substances, they divide themselves into fine ramifications which penetrate the cortical substance. From this it follows that the cortical substance is far richer in blood supply than the medullary substance. The thymic veins usually follow the course of the artery; group themselves into larger vessels; and empty into the left innominate, the pericardiophrenic, the mammary, and the thyroid veins. A point worthy of attention is that the arterial supply seems to be richer than the venous drainage. Furthermore, the thymus taking its blood supply directly off the large thoracic vessels, must

naturally be influenced by all the fluctuations in blood-pressure taking place in the great arterial system. Thus temporary swelling of the gland might be explained.

**Lymphatic Vessels.**—In 1665, Bartholinus mentioned the existence of the lymphatic vessels of the thymus and Warthonus and Drelincourt, in the 17th century, were of the opinion that the lymphatic vessels of the thymus emptied into the subclavian veins. During the Middle Age there was a curious belief that the thymus produced a milky secretion emptying into the bloodvessels and serving as a food to the newborn.

His and Matsunaga have described lymphatic vessels going from the medullary substance toward the periphery and emptying into the follicular lymphatic spaces. Langer and Toldt claim that the lymphatic vessels follow the veins. Stöhr and Schridde, on the other hand, denied that the lymphatic vessels exist in the thymus, whereas, according to Rauber, they are numerous and large. Severanu, under the guidance of Waldeyer, made careful injections of the thymus and was able unquestionably to ascertain their existence. According to him, they follow the interfollicular and reticular spaces and empty into the retrosternal lymph nodes. They may be divided into three groups: the superior, the anterior, and the posterior groups. The superior lymphatic vessels empty into the one lymph node located in the neighborhood of the innominates; the anterior lymphatic vessels empty into the lymph node situated in front of the thymus while the posterior lymphatic vessels empty into the lymph node situated between the thymus and the pericardium and the superior thymic lymph node empties into the subclavian vein. The anterior and posterior lymphatic vessels also empty into the subclavian vein and into the bronchomediastinal and venous trunks. Inasmuch as Hammar, too, without injections was able to ascertain the existence of such lymphatic vessels in the thymus, we may consequently say that the thymus, like the thyroid and adrenals, possesses a closed lymphatic system in which the organ empties its secretion and which finally reaches the blood circulation.

**Nerve Supply.**—The nerve supply seems to be mostly of sympathetic origin, as demonstrated by Hallion and Morel. That the vagus supplies the gland, too, has not been determined with certainty. According to Bovero, the nerves follow the interlobular septa and penetrate the medullary substances. So far, no nerves have been discovered in the cortical substance.

### CHEMISTRY OF THE THYMUS.

Chemical analysis of the thymus shows substances in the following proportions:

FRESH THYMUS.		
	By Bang, per cent.	By Lilienfeld, per cent.
Water . . . . .	80.41	88.51
Solid matter . . . . .	19.59	11.49
Total albumin . . . . .	19.92	9.10
Nucleoproteid . . . . .	1.08	8.90
Nucleohistone . . . . .	3.15	
Alcoholic substances . . . . .	2.48	1.83
Ash . . . . .	1.59	0.00

DRIED THYMUS.		Lilienfeld, per cent.
Albumin . . . . .		1.76
Leukonuclein . . . . .		68.78
Histone . . . . .		8.67
Lecithin . . . . .		7.57
Fat . . . . .		4.02
Cholesterin . . . . .		4.40
Glycogen . . . . .		0.80

A glance at the above analysis shows at once that the phosphorus content of the thymus gland is exceedingly high. It is present under the form of nucleoproteid and nucleohistone, the whole phosphorus content being contained in the acid nucleinates. The radical histone seems to be typical of the thymus. The phosphorus content of the nucleoproteid is 0.43 per cent while that of the nucleohistone is 3.25 per cent. Furthermore, Scherer found in the thymus purin bases, xanthine and hypoxanthine. It is not yet certain if these substances are products of decomposition of the nucleins, or if they are synthetic substances used up in the organism to form nucleins. Very small amounts of lactic acid, formic acid and salts of ammonia have also been found in the thymus. The aqueous extract of the thymus contains an enzyme which splits up the acid nucleins. It is known as *Schittenhelm's nuclease*.

Consequently, it would seem that one of the most important functions of the thymus is the metabolism of phosphorus in the organism. How this takes place is not yet certain. The metabolism of phosphorus in the thymus may be compared with the metabolism of iodine in the thyroid.

## EXPERIMENTAL PHYSIOLOGY AND PATHOLOGY OF THE THYMUS.

In 1845, Restelli undertook a series of 98 thymectomies in lambs, dogs and calves. Ninety-two died during the operation and the remainder in the following nine to twenty-three days. Despite this tremendous

mortality Restelli saw enough of the clinical picture to observe that the dogs not only had an unusual but a perverted appetite, inasmuch as they ate straw, hooves, dog flesh, and even their own penes. He sought to make a complete thymectomy by using the intrathoracic route, dividing the sternum in the middle line. As our modern asepsis was unknown to him, it is no wonder that his mortality was so high. Furthermore, in the light of our present knowledge concerning thymus experimental pathology, it is not doing injustice to Restelli to assert that his thymectomies must have been grossly incomplete.

In 1858, Friedleben undertook to repeat Restelli's experiments, but instead of going through the sternum he attempted to remove the thymus through the superior opening of the thorax. By careful dissection he was able to pull the thymus piecemeal out of the mediastinal space. In few instances, he thought that he succeeded in removing it all, but in the majority of cases he performed only a partial thymectomy. In many instances, thymectomy was accompanied by splenectomy. Most of the animals died from sepsis. In one case he observed that the dogs showed exaggerated hunger and that the bones grew very fast. He concluded, however, that from his point of view the thymus was not essential to life and that thymectomy was more or less harmless. In his judgment, splenectomy was far more harmful, but in both conditions the mortality was mostly due to infections. He regarded the thymus as an organ concerned with blood formation, nutrition and growth. It is not necessary to say that his experiments, although very interesting, are not convincing because his thymectomies were only partial.

In 1893, Langerhans and Saveliew undertook experimental thymectomy in guinea-pigs. There, too, the thymectomy was complete in only one animal, so that their conclusions cannot be regarded as based upon complete experimental facts.

Thiroloux and C. Bernard, in 1894, observed that after thymectomy the animals lost flesh, experienced tetanic convulsions, accompanied with high temperature, and died three or four weeks after. Autopsy showed marked pulmonary hemorrhages. Langerhans, Saveliew, Gluck, Carbone, Ghika, Cozzolino, Basch and Fischel were unable to obtain the same results.

From 1894 to 1898, Tarulli and Lo Monaca observed that after thymectomy performed in dogs the animals showed marked nutritional changes such as loss of flesh, loss of strength, coarse hair, diminution of red cells, and increase in the number of leukocytes accompanied by a transitory eosinophilia. These investigators sought to perform complete thymectomy by opening the thorax in the middle line.

In 1896, Treupel, after thymectomy performed in dogs, observed marked tonic and clonic contractions which may remind one of tetany



observed in parathyroidectomy. Most likely, in his experiments Treupel had also removed the parathyroids.

In 1896, Abelous and Billard repeated the same experiments upon frogs and observed marked dynamic, trophic and blood changes. Twenty-four hours after thymectomy, marked muscular asthenia followed by progressive paralysis was observed. No lessening, but rather exaggeration of sensibility occurred. The trophic disturbances were characterized by ulcerations, subcutaneous hemorrhages, etc. The wounds showed no tendency to heal. The blood showed hydremia, diminution and swelling of the red corpuscles, with increase of leukocytes, and finally a general edema took place with subcutaneous hemorrhages. A unilateral thymectomy did not cause any such symptoms, but if later on the other thymus was removed, then the clinical picture just described would become acute, and from four to fifteen days after the frogs died. If an interval of two or three weeks was left between the unilateral thymectomy and the removal of the second lobe, then the latter was found markedly hypertrophied. In Abelous's and Billard's judgment, the thymus acted as a detoxicating organ; the thymus was supposed to destroy some toxic products of the metabolism. Suppression of the thymus caused autointoxication and finally death. Their view was strengthened by the fact that injection of thymic extract, although not preventing death, mitigated the thymic cachexia to a great extent.

In 1897, Carbone did not see any untoward effects of thymectomy upon dogs or rabbits.

Abelous's and Billard's results were rejected by Ver Eecke in 1899, and similar experiments were absolutely negative with Parri, who in 1905, interpreted the results obtained as due to the diminished resistance to infection, because what he most observed were local infections. He admitted that thymectomy rendered animals more susceptible to infection.

In 1900, Camia confirmed Abelous's and Billard's results.

In 1901, Ghika after performing thymectomies in cats and guinea-pigs observed a progressive loss of flesh and blood changes. These results, however, were observed in only a few animals; some of them recuperated after a while, while some others remained entirely unaffected.

In 1903, Cozzolino observed that thymectomized rabbits had a diminished resistance to diphtheria toxin. Furthermore, as he observed that two or three months after thymectomy marked signs of rickets occurred in the limbs of the animals, he naturally regarded this condition as due to thymectomy.

In 1904, Sinhuber was unable to see any relation between thymectomy and rickets. In 1904, also, Swale Vincent made experiments in guinea-

pigs without any untoward results. However, the animals seemed to be less resistant to infection. In the same year, Noël Paton and Goodall observed a diminished resistance in the thymectomized guinea-pigs toward diphtheria, staphylo- and streptococci toxins. Hart and Nordmann observed extensive skin affections and suppurations after thymectomy. The general consensus of opinion of these workers has consequently been that the thymus is a detoxicating organ, and that it offers active and passive resistance against infections and infectious diseases. This, however, is by no means certain. Most likely, the diminished resistance toward infection was due to the depressed condition of the animals and not to a specific property of the thymus.

Hammar, in 1905, obtained negative results and concluded after a long series of experiments that the thymus in frogs as well as in mammals is not an organ essential to life.

In 1906, Fischel experimenting on goats three or four weeks old could not see any relation between thymectomy and the healing of fractures. The healing was not retarded nor accelerated. The same author experimenting on dogs and rabbits three to six weeks old came to the same conclusion. The osseous system, in his judgment, is not influenced one way or the other by the thymus.

The first really very systematic experiments were made on dogs from 1903 to 1908 by Basch. He selected dogs from the same litter to be used as subjects and controls. His observations were mostly directed toward the effect of thymectomy upon the osseous system. He observed that three or four weeks after extirpation of the thymus the bones became soft and pliable, especially the femur. The dogs' walk became uncertain and they lost flesh and showed marked progressive asthenic symptoms. The epiphysis of the radius became larger while at the same time the growth of the animals seemed to be greatly retarded. The mental condition of the animals altered entirely. They lost their intelligence and assumed a stupid look. In fractures he observed that the callus formation was markedly retarded when compared with the control animals. This he attributed to the lessened production of callus. With *x*-rays he was able to ascertain a diminished ossification which, in his judgment, was due to defective assimilation of calcium. He concluded that calcium is eliminated in the urine in greater amounts and that this eliminating process goes on for a long time, having as a consequence a retarded growth of the bones, thinning of the cortical substance, vacuolization and spongy aspect of the medullary spaces, irregular but enlarged epiphyseal line, all being but the logical results of the calcium deficiency. In short, these findings are very similar to those observed in rickets.

Matti, in 1912, repeating the experiments of Basch came to the same

conclusion. In his judgment the conditions observed in the osseous system were entirely similar to those found in rickets, although he did not go so far as to make the statement that the condition seen after thymectomy and the ones seen in rickets have the same etiology. He observed the same loss of flesh, the same muscular asthenia, the same metabolic disturbances as described by Basch. Thymopriva cachexia is a very well-defined clinical picture in his judgment. The osseous disturbances are due to a defective metabolism of calcium and also to disturbances of the endochondral ossification. Matti concludes that the thymus is an organ essential to life.

In 1912, Klose and Vogt gave the results of their thymectomies. They established first the fact that the animals best suited for such experiments are dogs, and that the propitious time to perform thymectomy is between the tenth and fourteenth days. At that time the thymus has not yet grown adherent to the organs of the thorax and can be easily removed. One of the most important prerequisites is to be sure that the thymectomy is complete, because a failure to do so, or to leave behind a small particle of thymus, may jeopardize entirely the results of the experiments, inasmuch as thymic compensatory hypertrophy takes place with the most astonishing rapidity, thus offsetting the lost function of the removed thymus. This occasions a complete blur of the clinical picture. That is why the results of thymus insufficiency are less, or not apparent, in animals in which thymectomy has been performed in a later stage of life. In such cases it is practically impossible to remove all the gland. The operation must be performed with the greatest care and the greatest rapidity. Ether is used with the "Meltzer positive pressure" apparatus. Morphine ought to be avoided on account of the respiratory disturbances which it is likely to cause. The sternum is divided into two portions, and thymectomy is then performed with the greatest care so as to avoid leaving any particles of the thymus behind or injuring the thoracic organs.

Klose first described a latent stage during which there is rather an increase of adipose tissue. This stage is called by him *stadium adipositas*, or *stage of adiposity*. Fatty degeneration takes place especially in the mesentery, subcutaneous tissues, testicles and ovaries. This stage lasts two or three months. However, a close scrutiny will show that the affected dogs have less muscular resistance than the controls. One fact worthy of observation is their increased appetite. The thymectomized animals eat twice as much as the controls.

Then three or four months after thymectomy comes the second stage. It is characterized by a marked muscular weakness, osseous disturbances and tremor. The little animals lose flesh and stop growing. Their bones become elastic and spontaneous fractures are frequent. Their

walk becomes uncertain and as soon as they move they are out of breath. The teeth formation is bad. They perspire freely and lose their hair. The tremor is composed of rather coarse tremulations. Their appetite still remains enormous and perverse; they eat stones, cork, and even their own penes. Edema and ulcerations of the skin, and especially ulcerations of the cornea leading frequently to blindness, are present. This stage is called by Klose the *stadium cachecticum*, or *cachexia thymopriva*. These animals usually die during the stage of unconsciousness which Klose calls *coma thymicum*. The duration of cachexia thymopriva lasts several months and may extend to fourteen months.

The metabolic disturbances observed in thymectomized animals seem to be very marked. The nitrogen excretion especially is increased but does not seem to be changed in quality. We already have seen that Basch found that four or five weeks after thymus extirpation the excretion of calcium was increased. Bracci came to the same conclusion. He found, furthermore, an increased calcium content of the blood and diminished calcium content of the bones, of the nervous system, and of the muscles. Soli made the same observations. The body temperature of thymectomized animals seems not to be influenced.

According to Klose, the mode of healing of fractures of thymectomized animals does not follow at all that seen in normal animals. After three weeks the fracture of a normal animal is, so to speak, healed while in thymectomized animals the fracture is still mobile. After five weeks in normal animals there is a distinct callus, whereas in thymectomized animals the fracture is still as mobile as it was fourteen days after the fracture, and remains so for a long time. Fragments are held together only by a fibrous callus, or by some osteoid formation very poor in calcium content. Klose finally concludes that the pathological, histological, and chemical conditions found in bones after thymectomy are the same as those seen in rickets and in osteomalacia. Fundamental in all these conditions is osteoporosis, which is due to a deficient quantity of calcium content in the bone. The only real difference observed is that in thymectomy there is a deficient formation of the bones, whereas, in rickets, and especially in osteomalacia, we have a marked absorption of the bony constituents.

Beside the osseous disturbances described by Bracci and Matti, as elasticity, softness, diminution of calcium content, slow tendency to heal, spontaneous fractures, etc., Klose observed that the cortical substance of the bones was much reduced, and noted especially that the medullary contained cysts. He called attention to the fact that spontaneous fractures occur regularly at the site where these pathological cysts are located. These cysts are varied in size, some being as large as a hazelnut. In his judgment, spontaneous fractures are mostly due to the



osteoporotic condition of the bones and to the presence of cysts which involve not only the medullary spaces, but encroach upon the cortical substance of the bones. To the objection that osteoporosis is not necessarily the result of thymectomy because it is present too in other experimental operations upon animals, as observed, for instance, by Pawlow after numerous experiments upon the pancreas, and by Fischler and Looser after experimenting upon the gall-bladder, Klose answers that these osseous disturbances are constant in thymectomy, whereas in other experimental operations they are rare. Furthermore, they occur at a certain definite period after thymectomy. This relation between the time of thymectomy and the appearance of the disturbance is very constant. Finally, these disturbances show no tendency to decrease, but rather go on increasing until death occurs. Chemistry of the bones of thymectomized dogs shows a great diminution of phosphates, and especially of calcium salts. The calcium content is about one-fourth to one-fifth of what it should be. For all these reasons Klose considers these disturbances as of thymic origin.

In accord with Basch, Klose and Vogt observed considerable changes in the nervous system of thymectomized animals. The ganglia cells of the brain are abnormally large, pale, and have an indefinite and irregular contour. The cells appear as if used up. Nissl bodies are irregular, atypical and opaque. The cerebellum, medulla, central ganglia, and the medulla oblongata show nothing abnormal. Vacuolization of the peripheral nervous system is one of the main features. The adventitia and bloodvessels of the brain show a desquamation and swelling of the endothelium; furthermore, infiltration of lymphocytes and plasma cells are found in the walls of the bloodvessels. The muscularis of the vessels is usually intact. At the same time the peripheric nerves and bloodvessels show a more or less marked edema. This swelling of the nervous elements is due to an increased retention of water among the elements, most likely due to an increased acidity of the blood cells. This acidosis may be caused by an actual increase of the acid contents of the blood, or may be due possibly to the absence of the substance destined to counterbalance the acidity. This speculative fact is exceedingly interesting, and if true, would prove of practical importance, because, as we know, acidosis frequently follows operations for thyrotoxic goiter and is always a dreaded complication, since it often terminates in coma and death.

Pathological changes are observed too in the muscular system. After a certain period of time thymectomized animals show an extreme muscular weakness and tremor. The muscles have lost their striation; their sarcolemma and external permysium have become thickened and swollen; the muscular fibers are atrophied; the connective tissue is very

much increased and swollen; the actual content of the musculature is manifestly decreased.

At first, these findings seem to throw some light toward a satisfactory explanation of the muscular symptoms seen in thyrotoxicosis. Indeed, muscular asthenia seen in such conditions is exceedingly marked. It would seem from the above that most of these muscular symptoms seen in thyrotoxicosis are due to thymus insufficiency, yet it is a well-known fact that in thyrotoxicosis the thymus, instead of being atrophied, is hyperplastic. On the other hand, we know that myasthenia gravis is often accompanied by thymus hyperplasia. The musculature in such cases shows marked pathological changes such as round-cell infiltration, fatty degeneration, etc.

As regards the effects of thymectomy in white rats, Magnini, in 1913, and Klose, in 1914, obtained results comparable to those found by Klose in dogs.

Thus, despite the negative and contradictory results of some investigators, nevertheless owing to the thorough and scientific researches of Matti, Basch and especially of Klose and Vogt, some of the physiological aspects of the thymus gland seem to be established on a firm basis. Subsequent researches, however, made by other investigators have opened up anew the whole question for discussion.

Thus, Nordmann, in 1914, operating on dogs between the tenth and fourteenth days, using strict asepsis, tracheal insufflation, wide exposure of the mediastinum and strict histological control as to the completeness of the operation, produced neither nutritional nor skeletal changes. There was no increased susceptibility to infection, no correlated effects upon the sexual glands nor spleen; and contrary to the statements of Klose and others, subsequent splenectomy in these animals was well borne.

Pappenheimer, in 1914, studied the effects of thymus extirpation in albino rats. One hundred and eight were used. Of these 82 were thymectomized and the remainder served as controls. Pappenheimer found that removal of the thymus does not produce any arrest or retardation of the body growth or development. Qualitative changes in the teeth are not found. In emaciated, weak animals osteogenesis is less active than in the healthy rats and the long bones are smaller and more delicate in structure. Such quantitative differences appear to depend upon the general nutrition and are equally pronounced in rats whose development is retarded from other causes and cannot be referred especially to loss of thymus function. No constant or characteristic changes are detected in the spleen, adrenals, testes or thyroid. Furthermore, he found that the relative proportion of lymphocytes in the blood is diminished the first few weeks after operation. When the rats were

killed 185 days after operation, minute seriated examination of the neck organs failed to show any tissue which could be interpreted as thymus tissue.

Halnen and Marshall, in 1914, found that extirpation of the thymus gland in young animals had no effect upon their growth even when the testes were simultaneously removed.

Howland, McClure and Park have for several years been working on this problem. In 1916, they also obtained negative results. They, as well as Nordmann, have been alive to the importance of keeping their animals under hygienic conditions.

In 1916, after experimenting on guinea-pigs, Park said that his results in these animals were wholly negative; he showed, however, that the almost constant presence of accessory thymus tissue in the guinea-pig makes the animal unsuitable for determination of the question as to whether the presence of thymic tissue is essential to life.

Renton and Richardson, in 1916, repeating Klose's experiments, concluded that thymectomy of itself is not the real cause of the bony disturbance observed in selachians. In their judgment thymectomy does not make young animals more susceptible to spontaneous rickets, and if they do develop it, they do at the same time and in the same manner as the controls. The British investigators sum up their findings by concluding that the removal of the thymus cannot be held responsible for the bony changes in thymectomized animals.

Tongu, in 1916, repeated Klose's experiments and came to the following conclusions:

- I. Body weight. No change after thymus extirpation.
- II. Growth. No three stages as reported by Klose and Vogt.
- III. Nervous, psychic, etc. No effect.
- IV. Blood corpuscles. No change in the number of differential count.
- V. Change in opsonin index, none. The alexin action of the blood serum is lowered for several weeks and then recovers, probably due to the activity of other alexin-producing tissues, bone-marrow, spleen, etc.
- VI. Blood-pressure, results conflicting.
- VII. Histological. There were generally small patches of thymus cells in the body, due either to regeneration or accessory thymus-granular structures.
- VIII. Skeletal changes. No change in length, cellular structure, calcium content or callus formation after fracture of epiphysis.
- IX. Change in the other organs. No change, macroscopic or microscopic, in any of the other internal organs, epithelial tissues or lymphoid tissue.

On the whole this evidence apparently convincingly indicates that the thymus is not an organ of internal secretion.

As Item No. VII indicates that small patches of the thymus cells are found in the body, it may still be said that thymectomy in these cases was not complete, consequently, Klose's results are not disproved.

Extirpation experiments in guinea-pigs undertaken by E. A. Park, in 1917, show that this animal is unsuited for experimentation on account of the accessory thymus often present. In his judgment, the experiments made by previous investigators using the guinea-pig, as a subject, must be regarded as partial extirpations and the results interpreted in that light. In his experience extirpation of the thymus in the guinea-pig produces no changes.

Allen, in 1918, claimed that he succeeded in removing the thymic "anlage" from young frog larvæ and observed that these larvæ grew enormously and underwent the usual development at the normal time. The results upon the spleen, however, are not given. The only question which may rise in one's mind is, How far did he succeed in completely removing the thymic "anlagen?" Knowing how difficult it is to perform a complete thymectomy in large animals, one cannot help being somewhat skeptical about the completeness of this operation. Gudernatsch, in 1914, Romeis and Abderhalden, in 1915, found that the thymus of the larvæ only delayed their metamorphosis; it did not impair their growth.

Finally, in 1919, came Park and McClure with a large monograph stating in detail their *modus operandi* and their results. They availed themselves of all the facilities that modern experimental surgery offers; their technic and their care for detail seem to have been faultless. The animals chosen were dogs, only two or three weeks old, as advocated by Klose. Efforts at complete thymectomy were faithfully made, and nearly always succeeded, as shown by seriated microscopical slides of the mediastinal fatty tissues suspicious of containing restes. The experimental results were always checked with control animals. A period of from one to fifteen months was allowed to elapse before sacrificing the animals. Seventy-five thymectomies were performed. They conclude as follows:

"The thymus gland is not essential to life.

Extirpation of the thymus produces no detectable alteration in the hair, teeth, contour of the body, muscular development, strength, activity or intelligence of the experimental animals.

Extirpation of the thymus probably does not influence growth or development. The possibility that it may cause retardation in development, or delay closure of the epiphysis, however, cannot be excluded absolutely.

Extirpation of the thymus probably produces no alterations in the organs of internal secretion. It is possible that it produces well-marked changes in the organs of internal secretion in the time immediately following thymectomy which is not covered by our experiments."



Renton and Robertson, in 1917, repeated Klose and Vogt's experiments totally removing the thymus in 8 puppies from thirteen to twenty-five days old. They were kept for varying periods up to several months. Not the slightest effect ascribed to loss of thymus was observed.

**Feeding, Injecting and Transplanting Experiments.**—Injection of thymus extract in the blood stream as done by Svehla produced a marked sinking of the blood-pressure. Of course, today we know that this property of lowering the blood-pressure is not the appanage of the thymus alone but belongs to most of the animal extracts, as shown by Bingel and Strauss, in 1909, and corroborated by many other investigators since. This depressor substance seems to act as a vasodilator, and although its chemical nature is not certainly known, it is probable, according to Dale, Laidlow, and Barger, that it is a B-iminazoly-ethylamine. As Biedl says, "The physiological activity shown by an extract of an organ is in itself no proof of any internal secreting function."

Gouin and Adouard after an injection of thymus extract in lambs observed an increased diuresis.

Swingle fed fresh thymus and the commercial powdered thymus to 250 frog larvæ. The thymus had no effect upon the growth nor upon the metamorphosis of the larvæ as compared with those liver-fed. The gonads were not affected, consequently, the author concludes that the thymus has no effect upon frog larvæ.

Shimizu, in 1914, immunized rabbits against dog thymus and used the thymus-immune serum in studying thymus function. Fifteen dogs were treated with the thymus-immune serum. All showed more or less of the toxic phenomena which corresponds to those of primary anaphylaxis. Twelve showed distinctly typical change of thymus, namely, decrease in size of the thymus gland, atrophy of the medullary substance, and increase in growth of the connective tissue. In 2 cases a high-grade atrophy of the thymus was noted. Aside from these anaphylactic phenomena, the use of the thymus-immune serum in dogs brought about a widely distributed destruction of thymus tissue, while normal rabbit serum as well as immune serum obtained from the spleen of dogs showed no characteristic destructive influence upon the thymus. The author concludes that the thymus-immune serum is specific and indeed contains a thymus-destroying body, a "*thymo-lysin*" causing distinct atrophy of the medullary gland. These researches might lead to the conclusion that the cortex of the thymus and the medulla of the thymus have biologically entirely different functions, and that the internal secretory function of the thymus is confined to the medullary substance.

In 1914, Yokohama was able to eliminate or lessen the action of adrenalin on the blood-pressure through injections of extract of thymus, showing that the action of extract is hypotonic.

Williams and Crowell, in 1916, record some observations made in the course of other experiments as to the atrophy of the thymus in cases of beriberi. In four beriberic pigeons which had been fed on white rice, the thymus had completely disappeared in every case. Examining 16 chickens in which polyneuritis had developed as a result of white rice diet, it was found that the thymus had completely disappeared in 7 cases, was considerably changed in 5 other cases, and apparently was only slightly, if at all, changed in the other 4 cases. That this atrophy is not caused simply by the age of fowls is shown by the fact that it happened in those that were fullgrown. No relationship could be established between the atrophy of the thymus and the length of the incubation period or the duration, severity, or specific symptoms of the disease. Four chickens which had been fed on milk and white rice for varying periods in the course of another experiment were examined after death. These chickens had shown signs of neuritis and were killed. Their sciatic nerves showed microscopic evidence of degeneration in Marchi preparations. The thymus of one fed with autoclaved milk and white rice was small while the thymus glands of the other three chickens which were fed on milk and white rice were larger.

Two fowls were fed on white rice with an addition of 10 grains of dried sheep's thymus daily. It was calculated that the quantity of thymus tissue ingested during the normal period of incubation would be the same as that normally present in young fowls. This small amount of tissue noticeably retarded, but did not prevent the onset of the disease. Two fowls were fed on white rice daily with a dose of alcoholic extract of 1.5 gram thymus gland. Here again the protection was not complete although the loss in weight and the onset of the disease were retarded. Two fowls were fed in the same manner but with a daily dose of the extract of 3 grams of thymus with less protective results. For comparison, two fowls were fed on white rice and 2 grams of uracil daily. One contracted chicken cholera, and the other was apparently partially protected by the uracil. Five fowls suffering from polyneuritis were treated with a hydrolized extract of thymus gland in doses of from 5 to 50 grams of the gland. No cures were obtained. Two human cases of beriberi were treated with small quantities of thymus and a slight improvement was seen in each case. This improvement did not last after the first few days of treatment and the patient at the close of the treatment still showed the characteristic symptoms of the disease, although in a less distressing form. The dose was 0.3 gram of dried sheep thymus six times daily. No change was made in the diet of the patient. (*Progressive Medicine*, June, 1916.)

Gudernatsch, in 1914, and Abderhalden, in 1915, found that feeding thymus to larvæ only delayed their metamorphosis, but did not retard

their growth. It must be said, however, that for feeding purposes they used thymus tissue from mammals. How far the biological chemistry and the physiological properties of the latter thymus differ from the one necessary to the frog larvæ has not yet been determined, but certainly there must be a difference as the frog larvæ normally undergo a metamorphosis which mammals do not.

Stettner, in 1916, repeating Gudernatsch's experiments, found that thymus feeding caused delayed metamorphosis, but not the growth described by Gudernatsch. Inadequate bone formation frequently resulted in crooked tails. The tadpoles also showed abnormal configuration suggestive to the author of rickets in children. Feeding with testes or ovarian material caused slight delay of metamorphosis but growth was normal and tails were not seen. Combined thymus and gonad tissue exerted no influence.

Hammar, in 1916, showed that feeding of the thymus gland to rats delayed development of testes in young males and caused degeneration of testes in adults; all the rats were sterile although ripe spermatozoa and ripe ova might be demonstrated histologically. There were no definite changes in the thymus itself.

In 1916, Renton found healthy thymus tissue up to fifty-three days after transplantation from one guinea-pig to another. The thymus was rapidly absorbed when transplanted to the peritoneum (abdomen and tunica vaginalis) but grew well on the subperitoneal tissues. No symptoms were caused by the transplantation of the thymus nor was it possible to determine if the transplant functioned even when it grew well. Total removal of the thymus did not cause any apparent symptoms in young guinea-pigs and rabbits.

According to Uhlenhuth, in 1917, salamander larvæ fed exclusively on thymus invariably developed tetany, the symptoms being the same as those produced in mammals by parathyroidectomy. Consequently, it was suggested that the thymus contains the substances that cause tetany and that it excretes them into the body from which they are removed by the parathyroids, and that extirpation of the latter would thus cause tetany. Tadpoles which develop parathyroids a few days after hatching have never been known to develop tetany when fed with thymus. Since salamander larvæ have no parathyroids, they at once exhibit symptoms of tetany on feeding with thymus but at metamorphosis when parathyroid glands appear, the tetany ceases. Tetany was never observed in metamorphosed salamanders even when kept on an exclusive thymus diet.

According to Swingle, in 1917, feeding thymus gland either in the fresh state or powdered form to frog larvæ of the species *Rana pipiens catesbiana*, does not accelerate the growth processes or retard metamorphosis of these



animals. Tadpoles seem to develop normally in every respect. The gonads do not seem to be affected by thymus feeding.

Olkon, in 1918, found that intraperitoneal injections of thymus preparations often caused muscular spasm, hysteria and convulsions. These spasms appeared to be more severe and of longer duration than those following injections of muscles of one-tenth normal sodium chloride solution. Emaciation, accompanied by dryness and roughness of fur, loss of weight, followed the continual use of thymus preparations.

Glaessner, in 1918, found that an injection of thymus hastens the healing of bones in rabbits.

As Müller had shown that a fatigued muscle of a frog acquires new vigor after being injected with thymus extract, Del Campo, in 1918, repeated these experiments with mammals and obtained the same results. If the sciatic nerve of a rabbit is stimulated every four seconds and the contractions of the soleus muscle are registered, the contractions soon become smaller and finally cease. However, they reach their original height again as soon as injection of thymus extract into a vein is performed. This extract does not seem to act on the muscle directly, but on the nerve, for when stimulation of the nerve does not cause further contractions, stimulation of the muscles still gives rise to a strong contraction. Therefore, Del Campo concludes that fatigue of a muscle is caused by exhaustion of the nerve and not of the muscle itself. Consequently, he concludes that thymus extract acts upon the nerve directly.

Uhlenhuth, in 1918, supplemented his report of the year before by stating that the condition of tetany produced in salamander larvæ by an exclusive diet of thymus, was shown to be due to a specific tetany toxin and not a dietary deficiency, since tetany also developed in animals that received earth worms in addition to thymus glands in their food. Thymus feeding also does not retard metamorphosis, as some believe, the retardation in such experiments being due to their restricted diet.

Finally, in 1918, Uhlenhuth found that, although thymus fed salamander larvæ often metamorphosed, on the other hand, thymus feeding sometimes retards and in rare cases completely inhibits metamorphosis. This action, however, is inconstant and variable, completely unlike the constant effects of the tetany-producing substances of the thymus. When animal food is added to the thymus diet the inhibitory effect does not follow. The addition of a small quantity of Bayer's iodothyron rapidly produces a precocious metamorphosis of the thymus-fed larvæ. Uhlenhuth consequently concludes that the inhibitory effect upon the thymus is not specific to the gland, but is due to the absence from the diet of the substances necessary to develop the thyroid into a secretory state.



## INTERRELATION OF THE THYMUS TO THE ORGANS OF INTERNAL SECRETION.

**Thymus and Thyroid.**—As shown by most investigators there exists an intimate relation between the thymus and the thyroid. After thyrmectomy the thyroids of animals used for experiment become manifestly hyperplastic; the follicles become larger, the epithelium higher, having the tendency to become cylindrical; in short, the thyroid gland shows in a general way the histological picture of the thyroid seen in Basedow's disease. The reverse is true, too, namely, that after thyroidectomy the thymus undergoes hyperplasia. This latter fact is also of great practical importance since it will allow us to understand why after an operation for goiter we may have to deal with mechanical as well as functional disturbances due to an increased thymic hyperplasia.

In 12 cases of thymic death in newborn, Hedinger found 7 cases with enlargement of the thyroid gland. In goitrous regions, especially in Bernese regions where goiter is endemic, thymus hypertrophy and struma in newborn are quite frequent.

In the Bernese Pathological Institute, 44 postmortems of newborn were made in 1910. In 12 of these cases thymus hyperplasia was extremely marked and the goiters were of large size. In the remaining cases the hyperplasia of the goiter and thymus, although quite marked, was not quite as pronounced as in the 12 cases just mentioned, and only in 3 instances were there concomitant goiters.

In adults this combination of thymus hyperplasia and goiter, especially toxic goiter, is extremely frequent, as has been reported by Virchow, Gluck, Wiens, Weber, Kaufmann, Rössle, Hart, Halsted and myself. This relation will be more fully discussed in the chapter: "Relation of Thymus Hyperplasia to Thyrotoxicosis."

Isaac Ott and Scott, by placing the thyroid gland in a metal oncometer, being careful not to disturb the anatomical relations of the gland with the surrounding structures, especially the bloodvessels and nerves, observed that infusion of thymus caused an enlargement of the thyroid gland. Arterial tension became lower for a couple of seconds, then returned to normal. The pulse rate was not changed.

Halsted reports the effect upon the thyroid of total excision of the thymus. In his judgment the histological picture presented by the thyroid seven months after total excision of the thymus seems to be identical with that obtained by Matti and Klose and interpreted by them as hyperplasia. The changes consist chiefly in the entire disappearance of the colloid and the great increase in the height of the cells.

MacLennan and Adler, observed thyroid hyperplastic changes fol-

lowing thymectomy. On the other hand, Pappenheimer, in 1915, Park and McClure, in 1919, reported negative results.

**Thymus and Adrenals.**—It is a very interesting fact, too, that after thymectomy the suprarenal bodies seem to undergo marked hyperplasia, whereas, in cases of thymic hyperplasia the chromaffin system seems to be decidedly diminished, hence, the conclusion that there is possibly an antagonism between these two systems. This relation, however, is by no means demonstrated yet, nor has it been shown beyond doubt that thymectomy influences the adrenals.

Boignet, Calogero and Matzoukis found that removal of the adrenals was followed by hyperplasia of the thymus. Wastinsen thinks the involution of the thymus may occur in consequence of the injection of extract of the medulla and adrenal cortex. Matti states that the medullary portion of the adrenals hypertrophies in dogs after thymectomy. Matti found that two animals with striking thymus hyperplasia following extirpation of the spleen showed an extraordinary diminution of the amount of adrenal medulla.

In 1919, Park and McClure denied finding any pathological alterations in the adrenals following thymectomy. No histological evidence of hyperplasia in the medulla of the suprarenals was found. In their judgment, thymectomy has no influence upon the adrenals.

**Thymus and Spleen.**—Klose reported that in thymectomized dogs the spleen is often hyperplastic. He believes that the spleen to a certain extent takes up the function of the suppressed thymus. He bases his belief upon the fact that if splenectomy be performed a few weeks after thymectomy has been done, cachexia and death are markedly accelerated, consequently, he considers the spleen as a vicarious organ of the thymus. We must remember, however, that various investigators have been unable to confirm these findings. If Laudenbach found after splenectomy a marked thymic hyperplasia, on the other hand, Petrone and Bagal were unable to confirm these results.

In 1919, Park and McClure were unable to discover any alterations in the spleens of thymectomized dogs.

**Thymus and Parathyroids.**—Few investigators seem to think that there is a marked parathyroid hyperplasia after thymectomy. In Uhlenhuth's experiments, in 1919, salamander larvæ of several species were fed exclusively with calves' thymus. At a certain stage of their development supposed to correspond to the functional establishment of their own thymi, tetany appeared in all the larvæ. But at a later period corresponding to the development of the parathyroid glands all tetany disappeared. It was concluded, therefore, that the mammalian thymus contains a substance which is capable of producing tetany when fed to the larvæ of salamanders. As soon as the parathyroids

develop, the symptoms of tetany disappear. In addition to this, the salamander possesses another mechanism, which during the larval period, inhibits the production of tetany by the animal's own thymus gland. In one species (*Ambystoma tigrinum*) this mechanism is sufficient to prevent tetany even when the larvæ are fed with thymus.

No alterations in the parathyroids were found by Park and McClure, in 1919, following thymectomy in dogs.

**Thymus and Genital Organs.**—Schridde observed that hypoplasia of the testicles in a child was accompanied by a marked hyperplasia of the thymus. Calzolari and Hammar, in 1898, Noël Paton, in 1904, and Goodal, in 1905, were able to retard the physiological involution of the thymus in dogs, rabbits and guinea-pigs by castrating them. Paton observed that the development of the genital system and conception took place earlier in animals that had been thymectomized. Henderson, in 1904, observed that the castration of cows retarded involution of the thymus. Klose came to the same conclusion in his experiments on dogs, likewise did Hart and Nordmann. On the other hand, Soli, in 1907, Lucien and Parisot, in 1908, came to the opposite conclusion. It seems, however, according to Klose that Soli's, Lucien's and Parisot's experiments were incorrectly interpreted by them because, if the testicles and ovaries of thymectomized animals are examined three or four months after thymectomy has been performed, they are invariably found hyperplastic. Still, according to Klose, the error of interpretation made by Soli, Lucien and Parisot was made because they examined the genital organs just before death when thymic cachexia had reached its highest and consequently must have involved the genital apparatus.

Henderson claims that physiological involution of the thymus takes place much more rapidly in animals during the heat period and during their first months of pregnancy.

Paltorti, in 1909, states that removal of the thymus in rabbits is followed by degenerative changes in the ovary, namely, a scarcity of primitive follicles in the outer zone and regressive changes in the follicles in the inner zone. Paton, in 1911, found that thymectomy in guinea-pigs was followed by hyperplasia of the testicles.

Klose and Vogt, in 1912, observed a transient hyperplasia of the testicles in thymectomized dogs followed by atrophy in the cachectic stage, but Matti, in the same year, obtained negative results.

Fulci, in 1913, reported that pregnancy in animals accelerated regression of the thymus and that after birth of the young, there was a distinct regeneration of the gland taking place. According to Bompiani, this regenerative process remains latent during the lactation period. Halnen, Marshall and Yale, in 1914, obtained negative results. Hatai, in 1905, found that gonadectomy not only delays thymic involution but often

causes a marked hyperplasia of the thymus also. Marine and Manley, in 1917, observed that autotransplantation of thymus in subcutaneous tissues of the abdomen survived in sexually immature rabbits. They came to the same conclusions as others, that removal of the thymus hastens sexual maturity.

Park, in 1917, using the guinea-pig, sought to revise the experiments made in order to determine the relation between the thymus and sexual glands especially in males. Careful study of seriated sections through the neck showed that the guinea-pig has so much accessory thymus tissue as to render complete thymectomy impossible. Consequently, in his judgment, early reports in these animals must be interpreted as partial only. After performing as nearly complete thymectomy as possible, Park did not succeed in detecting any difference between the experimental animals and the controls, either as to procreative activities, growth, or conditions in the various endocrine glands. No rachitic changes in the skeleton were observed.

In castrated cattle the thymus has been found to be double the size of that in uncastrated cattle. This holds true also for guinea-pigs, and in thymectomized guinea-pigs before sexual maturity, the growth of the testes is more rapid than normally. This phenomenon has also been found in dogs. It may represent a reciprocal inhibitory reaction of these glands, or if considered from the standpoint of influence on growth and development, it may be compensatory in nature. This question was tested by removing both thymus and testes in young guinea-pigs, with the result that after removal of both glands there was marked delay in growth, while removal of one or the other brought about no delay in growth. Heimann has noted that the secretions of the thymus and ovaries act in an antagonistic manner on the blood picture with respect to the number of lymphocytes. The testes and ovaries of thymectomized dogs according to Park and McClure, in 1919, show no essential difference from the testes and ovaries of the control animals.

All these observations and experiments seem to convey the conclusion that an antagonism exists between the genital system and the thymus. There occurs regularly following removal of the gonads before sexual maturity an unquestionable delay in the evolution of the thymus. This conclusion is strengthened by the fact that we know that the thymus undergoes atrophy at the time of puberty. Another proof of this contention, in Klose's opinion, is the mode of reaction of the osseous system toward castration and thymectomy; after castration the length of the bones is increased, whereas after thymectomy it is diminished. The latter fact, however, has not been confirmed. It has been generally understood that in cases of status thymolymphaticus the development of the genital apparatus is very much retarded, while on the other hand,



it seems that in young individuals whose genital system is prematurely developed the involution of the thymus occurs at an earlier period.

Between the thymus and the ovaries there seems to be experimental evidence for the possible functional antagonism. Paton, Soli, Klose and Vogt observed after thymectomy an increase in the weight of the ovary, while according to Tandler and Gross, there is an abnormal persistence of the thymus in eunuchs. Eppinger relates a case of Graves's disease in mild form in which immediately after castration toxic symptoms of threatened severity set in. Of like significance, probably, is the fact that during the climacterium a mild case of Graves's disease may be converted into a severe form.

Of further evidence of the antagonism between secretion of the ovary and the thymus may be mentioned the excessive lymphocytosis observed by Klose following the injection of Basedow thymus after ovariectomy. Injecting 5 cc of thymus juice expressed from the gland of a thyrotoxic patient into a spayed bitch whose lymphocytes after castration had risen to 32 per cent, Klose found the lymphocytes percentage had risen to 64 per cent at the time of death.

**Thymus and Pancreas.**—No changes in the pancreas were found by Park and McClure in 1919, in thymectomized dogs.

**Thymus and Pituitary.**—Maxwell, in 1916, showed that feeding of the anterior lobe of the pituitary body exerts a retarding influence upon the thymus. This retarding effect is not prevented by the administration simultaneously, of thyroid substances. After three months of administration of pituitary and thymus, postmortem examination showed the thymus was much smaller than in the one kept as control, hence the conclusion that there is a relation between the thymus and the pituitary body.

In 1919, Park and McClure were unable to report any alterations in the hypophysis of thymectomized dogs.

**Thymus and Metabolism.**—Ogata, in 1917, injected subcutaneously thymotoxic serum obtained from rabbits, immunized with dog thymus, into 9 dogs from ten to sixteen days old for a period of fifteen days. The controls received some injections of normal rabbit serum. Ogata reports that growth was retarded in the animals treated with the thymotoxic serum and that the thymus became atrophied and smaller, less dense and contained relatively more water and a smaller absolute amount of calcium oxide, magnesium oxide, and phosphoric oxide. The injection of serum of rabbits previously treated with ovarian tissue from the dogs produced no effect upon the thymus, thus indicating according to Ogata, the specific nature of thymotoxic serum.

**Is the Thymus a Hematopoietic Organ? Does it Take Part in the Formation of Red Blood Cells as Well as of Leukocytes?**—Schäffer

found in the thymus of cats and rabbits nucleated red blood cells. As these findings were constant, he concluded that red blood cells were formed in the thymus. Maximow, examining the thymus of embryo rabbits reported the same findings, the nucleated cells being erythroblasts and myelocytes. H. Fischer claims that red cells are formed in the connective tissue septa and in the meshes of the reticular cells. In his examination of thymi, Löw was unable to find any nucleated or red blood cells. The same is true of Naegeli. According to Schridde, the thymus does not take part in the formation of red blood cells. In his judgment, if nucleated red blood cells are found, they come from the perivascular tissue of the embryo.

So far as the formation of leukocytes is concerned, the matter stands as follows: Askanazy considers the thymus as a lymphoid organ producing lymphocytes. So does Beard. Dudgeon and Löw called attention to the great abundance of neutrophiles and eosinophiles found in the thymus. Schridde, especially, insists upon the great amount of eosinophile cells present in the cortical as well as in the medullary substance. In his judgment, they are mostly leukocytes; they reach their maximum about the eighth month of fetal life and disappear later apparently in direct proportion to the involution of the thymus. He is of the opinion that eosinophile cells are not produced *in situ*, but come from the blood stream because, in his judgment, they are polynuclear lymphocytes, and because, too, he was able to observe the passage of these eosinophiles directly to the walls of the bloodvessels. He believes, furthermore, that the eosinophiles diminish in direct proportion to the number of cortical cells and that on this account one is entitled to believe that eosinophile cells are of blood origin. Naegeli believes the same thing.

In the opinion of Fischer, the presence of such a great number of leukocytes and myelocytes in thymus is due to degenerative processes of the epithelium as well as of Hassal's corpuscles. The eosinophiles and leukocytes are then supposed to phagocyte the degenerated cells. Löw, on the other hand, is inclined to believe that eosinophile and myeloid cells migrate into the organ from the neighborhood. He insists, however, that because of their great number the mononuclears must take their origin in the thymus itself.

**Are Lymphocytes Produced in the Thymus?**—Naegeli and Maximow say, Yes. Naegeli claims that germinative centers are present in the thymus and that lymphoid tissue existed long before Hassal's corpuscles and the epithelium appeared. He regards the medullary cells as large lymphocytes, claiming that they are totally absent in the earlier period of embryological development and disappear in fasting conditions, a fact which would not occur if they were real epithelial cells. Schridde, on the other hand, claims that the germinative centers, spoken of by

Naegeli and Maximow, were due to mistaken observations and that they were only small portions of medullary bands of epithelium in which mitoses are very uncommon, the opposite being observed in lymphoid tissue. These medullary bands existed long before any germinative centers occurred in the lymphoid system. Mitoses are found in the cortical substances; no lymphatic sinuses are present. After experimental thymectomy the lymphocytes diminish very greatly, whereas the polynuclears increase, Klose believes that the thymus is not a *hematopoietic organ*, in sensu strictiori, but supposes that on account of its external secretion it may have an influence upon the organs whose function it is to produce blood corpuscles.

Tarulli and Lo Monaca found that after thymectomy in dogs and chickens a diminution of red as well as white corpuscles took place. The same findings were reported by Abelous and Billard. Ghika, experimenting on cats and rabbits, came to the conclusion that the thymus is a hematopoietic organ. After thymectomizing guinea-pigs Noël Paton and Goodal found a diminution of the red blood cells and of the white cells as well. Matti and Seiler found immediately after thymectomy a diminution of red blood cells and of the transitory leukocytes, but that later on the condition of the blood returned to normal. Klose, Lampe and Leisegang came to the conclusion that after thymectomy there is a progressive diminution of the leukocytes, whereas the intravenous injection of thymus juice causes a marked lymphocytosis. Bircher came to the same conclusion. Children with hyperplasia of the thymus usually have a marked lymphocytosis, whereas those with thymic aplasia have a marked hypolymphocytosis. This is corroborated by the thymectomies performed in children. After thymectomy the lymphocytosis falls far below what it was prior to the operation. To explain the lymphocytosis in cases of thymic hyperplasia, Klose resorted to the *dysthymization theory*, claiming that the thymus not only gives off an increased amount of secretion, but that it is also perverted.

¶ In 75 thymectomies performed by Crotti in conjunction with thyroidectomies for thyrotoxic goiter, the degree of lymphocytosis was as follows:

Small lymphocytes and large lymphocytes.	No.	Per cent total cases.
Under 35 per cent (differential count) . . . . .	29	38.6
Between 35 and 40 per cent . . . . .	8	10.66
Above . . . . .	38	50.66

Of this number the following were small lymphocytes:

Under 30 per cent . . . . .	27	36.0
Above 30 per cent . . . . .	48	64.0

61.33 per cent of the total number of cases showed marked relative lymphocytosis. The absolute leukocyte count varied only slightly from normal. Assuming a normal relative lymphocytosis of 30 per cent, the number of 75 thymus cases showing above that was 63, or 84 per cent of the total.

**General Summary.**—*Is There a Thymic Hormone?* The weight of evidence, at least thus far, is in favor of the lympho-epithelial nature of the thymus. To classify it without any further concern as a lymphoid organ, pure and simple, whose sole duty is to produce leukocytes, is a point of view still resting upon unsubstantiated physiological grounds. If one is willing to admit that the lympho-epithelial theory is not an absolutely demonstrated fact, he must, however, demand that better proofs be given him before he can admit with equanimity of soul that the thymus is a lymphoid organ pure and simple.

The physiological conception of the thymic function as established by Basch and Klose, has been severely jolted by Park and McClure and others, although the negative results obtained by many such competent investigators are open to criticism. In most of these experiments the essential prerequisite established by Klose, namely, *total thymectomy*, has not been fulfilled. In others it has been doubtfully met. The few experiments where one is reasonably sure that total thymectomy has been performed and where negative results are reported, do not seem to be sufficient in number to satisfy one's mind. Then, too, there is a difference in the interpretation of the results obtained with one school attributing the results obtained to thymic insufficiency, the other to dietetic and surrounding conditions. Before admitting that Basch, Matti and Klose have been so completely sidetracked, at best, one can only say that the whole subject of experimental physiology of the thymus must be taken up anew.

The same is true for the interrelation of the organs of internal secretion and the thymus. If it is true that there is strong evidence as to the interdependence of the thymus, the thyroid, and the gonads, the relation of the thymus to other glands of internal secretion is by no means so well demonstrated. There, too, is food for thought and investigation.

**Conclusions.**—Whether the thymus is a hematopoietic organ or not, is by no means yet clear. From our present day knowledge we may consider the participation of the thymus in the production of red cells as doubtful. That it is capable of producing lymphocytes seems to be probable. That it participates in the production of eosinophiles and other leukocytes is quite doubtful.

So far as the *thymic hormone* is concerned, it has not yet been isolated. The likelihood of its existence is purely circumstantial, and is based upon the assumption that the thymus plays a metabolic role not



well demonstrated by any means, but nevertheless rather probable. I say "probable," because in a general way the modern conception of the interworking of the organs of internal secretion is through hormones; because Klose's conclusions have not been refuted without recourse; because the thymus seems to metabolize phosphorus as the thyroid metabolizes iodine, and because, finally, Bircher seems to have been able to produce experimentally thyrotoxicosis in dogs by injecting thymus extract into the peritoneal cavity. Certain it is that the thymus has been put where it is by Nature for some purpose. It is well enough to assume that its sole duty is to produce leukocytes, but that this is really so, and only so, is still lacking in proof.

### PATHOLOGY OF THE THYMUS.

**Thymic Aplasia and Hypoplasia.**—The thymus may be found totally absent or markedly hypoplastic. Several authors seem to think that there is a causal relation between absence of the thymus, or even thymus hypoplasia, and mental disturbances in children. Thus, in 28 mentally defective cases Bourneville found the thymus absent. Furthermore, basing his conclusions upon a large number of autopsies of mentally defective children, he found that in 70 per cent the thymus was absent. Sajous believes that the deficient activity of the thymus results in deficiency of nucleins supplied to the brain through the lymphocytes, thus causing idiocy. Harrower, too, makes the statement that thymus hypoplasia is found in conjunction with defectiveness and with a hypoplastic type of individual.

**Pathological Involution or Atrophy.**—There are two forms of involution: the *physiological* and the *pathological*.

Physiological involution has been discussed in the chapter on Physiology.

Pathological involution may occur without any apparent cause, or may occur in conjunction with chronic conditions or infection such as marasmus, tuberculous empyema, etc. This pathological involution is most likely due to some intoxication or irritation centering upon the thymus and caused by the conditions above mentioned. Atrophy may become so marked as to obtain a complete sclerosis of the thymus. Adipose cells disappear, the arteries and veins show signs of endarteritis, the cortical and medullary substances can no longer be easily differentiated. The lymphoid cells are more or less absent and are replaced by fibroblastic and endothelial cells, resembling in many respects those found in Hassal's corpuscles. The eosinophiles are diminished. Hassal's corpuscles are somewhat increased and show retrogressive changes.

**Active and Passive Congestions.**—*Edema; Hemorrhages.*—*Active and passive congestions* of the thymus may occur under the most varied conditions; as a result, the thymus becomes enlarged and reddened. Such a congestive enlargement may be mistaken at autopsy for a genuine thymic hyperplasia. There is no doubt that such congestions play a very prominent part in the suffocation caused by thymic hyperplasia, as can be shown by postmortem. In many instances, however, autopsy findings are negative, because such suggestions have disappeared entirely, the gland appearing to be absolutely normal.

*Edema* of the thymus may be observed not only in generalized edema, but in localized conditions also, such as infections of the walls of the chest, and of the mediastinal space. When large saline injections are given in the pectoral region, just before death, marked edema may be found in the thymus.

*Hemorrhage.*—1. *Hemorrhagic Cysts of the Thymus.*—Already in 1614, Felix Plater, in his *Observationum in hominis affectibus* . . . *Basil*, reported a postmortem of a child five months old, who had died from suffocation and in which a hemorrhage was found, “carniforma quadam materia et sanguine oppleta.”

Ritter, in 1866 to 1871, collected out of the literature 190 cases of thymic hemorrhages, and Epstein, in 1875, had observed 61 cases.

In 1892, Raudnitz reported the case of a large hematoma of the thymus of a nine-days-old child, who up to this time had been perfectly well. The hematoma was developed in the right thymus and free blood was found in the thoracic cavity.

In a newborn, he reported another hematoma twice the size of a walnut, located in the left thymus, whereas, the right one was composed of the hematoma itself.

This condition was first called by Friedleben, “apoplexy of the thymus.” It usually occurs in newborn. It is characterized by sudden bleeding taking place in the thymus. It is not a parenchyma hemorrhage, but is a bleeding taking place in a preformed cavity composed of a wall with a distinct lining membrane, whose epithelium is usually flat, but which sometimes happens to be cylindrical, thus suggesting that the cystic cavity is due to remnants of thymic ducts. A coincidence of remarkable significance is that these hemorrhages occur usually in conjunction with congenital syphilis. At least, the cases reported by Barendsprung, Ritter and Raudnitz, Schlesinger, Mendelsohn, Bednar, and Sultan, were all syphilitic cases. Is there a relation of cause to effect between these two conditions? That is very probable and most likely the immediate cause of the bleeding is due to the rupture of some blood-vessel caused by luetic endarteritis.

2. *Diffuse Hematoma of the Thymus*.—This takes place in older children and in adults as well, and usually occurs in conjunction with acute diseases, although it may happen without any apparent cause. The hematoma is not limited by a well-defined membrane as in cystic hematoma, but permeates diffusely the thymic tissue, involving a more or less greater portion of it. In rare cases the whole thymus has been found involved; it appears then like a total infarctus of the gland.

3. *Punctated Hemorrhages of the Thymus*.—Small, punctate hemorrhages are frequently observed in the thymus of newborn and young children, dying from acute infectious diseases as whooping cough, pneumonia, hemophilia, convulsions, sepsis, etc. Dudgeon found punctated hemorrhages in the thymus in 95 per cent of the deaths occurring following bronchial pneumonia and lobar pneumonia. The same type is observed, too, in cases of difficult delivery especially in malpositions of the fetus followed with rotation, and forceps application. Attention to these cases was called by Weber, in 1842, and since then, various obstetricians have reported similar cases.

In 1909, Winkler reported a case of a four-days-old child who had undergone a forceps delivery, and who died four days after birth with symptoms of suffocation, although he had been apparently well up to that time. Postmortem showed a large hematoma of the thymus caused probably during the delivery. Another hematoma was observed in the right cerebral hemisphere, thus showing that the traumatic origin of the thymic hematoma was very probable.

Hemorrhage in these cases is characterized by a rather punctiform aspect involving the whole gland and extending to the neighboring structures, such as the pleura, pericardium, etc. The hemorrhagic point, however, may be as large as a pea, or larger. Under such conditions the thymus is much enlarged and has a firm consistency; hence, pressure upon the trachea and upon the mediastinal organs; hence, suffocation. Syphilis in these cases is not an etiological factor.

**Acute Thymitis.**—A primary thymitis has not yet been reported. The very rare cases so regarded are doubtful. On the other hand, acute thymitis, secondary to metastatic infections following some other acute focal process, has been observed more than once. Schridde, for instance, reported an abscess of the thymus following retropharyngeal abscess. The same was also observed by Hutinel and Tixier, Roger, Ghika and Klein after diphtheria and syphilis.

Pürkhauer reported a case of a four-year old boy who died suddenly while in apparently good health, and who showed at postmortem a large thymic abscess which had ruptured into the bronchus. This case seems to be one of thymic abscess.

In 1914, McWalter reported a case of acute thymitis in a child,

twelve months old, who had previously been healthy. Within the previous eight days, however, he had developed at the suprasternal notch a swelling which later extended upward as far as the hyoid bone and spread laterally as far as the middle third of the clavicle on each side. A distinct dulness over the upper part of the sternum was present. The swelling was uniformly smooth, not hot, and not painful to the touch. There was no sign of suppuration. Although dyspneic, the child was by no means evidently ill, and no sign of another complication could be detected. The appearance of the child, rather than the gravity of the symptoms, alarmed the mother.

A solution of oil of wintergreen in almond oil, 20 per cent, was applied to the swelling. Rapid improvement was being observed when the child suddenly ceased to breathe and death occurred suddenly and painlessly about the fourth day of the treatment. Unfortunately, postmortem was not secured, consequently, unquestionable proof that this was a case of real acute thymitis is lacking.

The microorganisms most frequently found in thymic abscesses are the staphylococcus, the streptococcus and the colon bacilli. Metastases take place through the hematogenous route. Localization of the abscess may take place either in the parenchyma or in the existing cysts. Diagnosis in these cases is made by taking into consideration the pressure symptoms due to tracheostenosis, the temperature, pain, pressure upon the sternum, leukocytosis and polynucleosis. X-ray may be of value. These abscesses are usually located in the mediastinal portion of the thymus; any surgical attempt to relieve the patient is consequently difficult and dangerous. It is, however, the only hopeful means of giving the patient relief.

**Acute Infections and Thymus.**—That in acute infections the thymus undergoes hyperplasia was noticed by Herard, in 1847, who based his conclusions upon sixty postmortems.

In 1858, Friedleben reported that the thymus in acute infections becomes, on the average, about three times larger than normally, whereas, in chronic conditions it undergoes a marked atrophy.

In 1888, Jacobi made a microscopical examination of 9 cases who died from acute infections such as diphtheria, bronchopneumonia, and in 2 cases only he found necrobiosis of the lymphocytes characterized by various stages of degeneration.

In 1894, O. Hausen reported the results of his examinations of 16 postmortems whose deaths were due to diphtheria. He found an enlarged thymus in each case.

In 1894, Mettenheimer examined 13 cases of diphtheria and 5 cases of scarlet fever, and came to the conclusion that in acute infections the thymus undergoes involution instead of hyperplasia. Microscopically,



he found hyperemia of the thymus but did not find the same degenerative changes of the cells, such as described by Jacobi.

In 1900, Roger and Ghika made some experimental researches to see how the thymus would react toward infections and at the same time examined the thymus in patients dying from acute infectious diseases such as scarlet fever, varioloid, diphtheria, erysipelas, pertussis, tuberculosis and syphilis. Experimentally, by injecting virulent cultures of streptococci, staphylococci, colon bacilli and Löffler bacilli, they were able to produce in guinea-pigs, the same pathological changes as observed in acute infections, *i. e.*, hyperplasia of the thymus, congestion, punctate, subcapsular and intracapsular hemorrhages. Microscopically, they found the walls of the bloodvessels hemorrhagic and infiltrated with leukocytes. The lymphocytes were quite numerous especially in the medullary portion and in the bloodvessels. Mono- and polynuclears, eosinophiles, neutrophiles, mast cells and giant cells were observed. The Hassal's corpuscles were increased in size and number and showed some retrogressive changes.

In 1901, Magni made cultures of the thymus of children who died from acute infections and was able to obtain positive cultures. It is his opinion that the thymus is more frequently involved by microbes than the liver, spleen, mesentery, etc.

In 1903, Francesconi studied experimentally the influence of microbic infections upon the thymus of guinea-pigs and found that the gland becomes hyperplastic; that the lymphoid elements, especially the medullary portions, become markedly increased; shows karyolytic changes; that the endothelium of the bloodvessels is swollen and that the connective tissue was infiltrated with leukocytes.

In 1904, Mensi repeated the same experiments and found that in 11 cases out of 26, the bacteriological examination of the thymus was positive. In 22 out of 26 cases, the Hassal's corpuscles were markedly increased in size and number and the eosinophiles were increased.

In 1904, Bracci studied the relation of the thymus to infections and observed that the Hassal's corpuscles underwent degeneration and that they were more or less transformed into small cystic nodules. At the same time, these Hassal's corpuscles were increased in number and size, so much so, that some of them were confluent and fused together to form a cavity. The connective tissue underwent a sclerosis. The parenchyma was separated by void spaces of various sizes.

In 1905, Fortescue and Brickdale examined 20 cases of children who had died from acute diseases such as pneumonia, diphtheria, peritonitis, etc., and found that in some cases involution of the thymus was present and that in some others hyperplasia had occurred.

In 1909, Ronconi, examining 2 cases of diphtheria, found an increased

volume of thymus and increase in the number of Hassal's corpuscles; in some others, however, he observed retrogressive changes in the thymus.

In 1910, Marfan in examining the thymus of patients who had died from diphtheria, erysipelas, variola, infectious purpura, etc., found a thymic hyperplasia with increased number and size of the Hassal's corpuscles and eosinophiles. The same findings were reported by Pappenheimer, in 1910.

Holdström reported the same findings in 1911.

K. Takeuchi studied experimentally the behavior of the thymus in acute infections in 57 rats; they were injected with colon bacilli. He did not observe, as is usually the case in human beings, any inflammatory hyperemia or hemorrhages of the thymus. He noticed that the cortical and medullary substances lost their normal differentiation. The thymic cells at first became hyperplastic, then showed degenerative processes and resorption, so much so, that in the last stage there remained only the connective tissue and Hassal's corpuscles. He did not observe any increase in the number and size of Hassal's corpuscles and of the eosinophiles, as happened in thymic infections in human beings.

In 1912, Hart reported the examination of 100 cases. He recorded the same findings, namely, in a great number of cases an increased hyperplasia of the thymus, increase in size and number of Hassal's corpuscles and increase of the eosinophiles. In diseases of long standing and of severe type, the damage done to the thymus is irreparable; pathological involution takes place and connective tissue infiltration invades the thymus, after which a fatty degenerative mass takes the place of the thymus.

In 1914, Oliari examining the thymus of 25 individuals who had died from various diseases such as tuberculosis, pleurisy, pneumonia, etc., observed hyperplasia of the thymus, sclerosis of the gland, and in a general way, marked regressive changes.

In 1918, Hammar reported the results of his researches of 21 cases who had died from diphtheria and came to the conclusion that in diphtheria the thymus undergoes an accidental involution in which more or less marked regressive changes are observed, but in which the number and size of Hassal's corpuscles are increased.

Furthermore, in examining the relation of the thymus to infectious diseases such as acute anteriopoliomyelitis, measles, scarlet fever, pertussis, typhus, typhoid, etc., Hammar, in 1918, observed that the thymus in a general way showed an increase in size and number of the Hassal's corpuscles. In diseases of long standing such as chronic tuberculosis, etc., the thymus underwent an involution and no increase in size and number of Hassal's corpuscles was observed. The same is true also in the case of hunger.

In conclusion we may say that the thymus reacts toward infectious disease mostly by an increased blood supply, by hyperplasia of the thymic elements, and by hyperplastic changes taking place in Hassal's corpuscles. In some instances, however, pathological involution instead of hyperplasia takes place.

**Sclerosis of the Thymus.**—In certain cases of malnutrition, of syphilis, of tuberculosis, the thymus undergoes a process similar to the one observed in atrophic cirrhosis of the liver and kidneys. There, too, we have a process of connective tissue formation, gradual in character, involving the cortical substance first and the medullary portion of the thymus afterward. In the terminal stage all that remains of the thymus is a small but hard mass involving the whole gland and firmly attached to the neighboring tissues. This sclerosis of the thymus in many respects resembles the one seen in the thyroid and called "woody thyroiditis." In rare cases, as reported by Klose, instead of having an atrophy we have an hypertrophy of the connective tissue so much so that this author is inclined to regard these cases as fibromata.

**Syphilis of the Thymus.**—Nothing is known of secondary syphilis so far as the thymus is concerned. Tertiary syphilis has been found once in a while and is characterized by gummata, which do not differ in any way from those seen in other organs. In hereditary syphilis, Paul Dubois, in 1850, described abscesses known since in the literature as the "Dubois abscess." These are not abscesses in the true sense of the word, but are due to the breaking down of the syphilitic gumma. Some pus is usually found. They always contain a large amount of spirochetes.

Chiari, in 1893, finding several so-called "Dubois abscesses" in the newborn, observed that on microscopical examination these abscesses were surrounded by a capsule composed of several layers of cells plainly keratohyaline in character. He concluded, therefore, that these abscesses originated in previously existing cysts. The contents of these cysts were composed of cells with large, clear nuclei, and small lymphoid cells. The keratohyaline character of the cells led him to conclude that the cysts took their origin primarily in a Hassal's corpuscle.

Beside these undoubted cases of syphilis, a number of statements are found in the literature concerning the changes found in the thymus as a result of congenital syphilis. Hyperemia, hemorrhage, sclerosis, endarteritis, cysts, etc., have all been ascribed to the reaction of the syphilis upon the thymus. How far syphilis is responsible for these conditions is not yet ascertained.

**Tuberculosis of the Thymus.**—Primary tuberculosis of the thymus is very rare. The majority of cases so reported are doubtful, because enough care has not been taken to ascertain if the primary focus was in the thymus, in the tracheobronchial glands, or in the lungs. About

the only case of undoubted primary tuberculosis of thymus is the one reported by Demme, that of a child whose parents were non-tuberculous. The child died the third month of general marasmus. Autopsy showed an enlarged thymus containing several tuberculous foci. Evidence of tuberculosis could not be found anywhere else.

Secondary tuberculosis of the thymus is more frequent, however, as a number of cases of tuberculosis of the thymus following a primary focus located in the neighboring organs such as the tracheobronchial glands, lungs, etc., have been reported.

In 1888, Jacobi examined about 100 thymi of tuberculous patients. In his judgment, tuberculosis of the thymus is not uncommon since he found it 3 times out of 60 cases in patients having died from any kind of disease, and found it in one-fourth of all the cases that died from tuberculosis. Tuberculosis occurs as a miliary or a caseous form. In all the cases he was able to demonstrate the presence of tubercle bacilli.

Carpenter reported the autopsy of a child, two years old, in whom a large tuberculous abscess was developed in the thymus gland. The tuberculosis had involved both lungs. In this case it is impossible to determine if the tuberculosis was primary in the thymus or only secondary. The latter alternative seems the more likely.

In 1909, Tixier and Feldzer performed an autopsy on a child, three years old, who had died of primary tuberculosis. Autopsy showed that the tuberculosis was localized to the lungs, the tracheobronchial glands, liver, spleen and kidneys. None was found in the brain. The thymus was studded with tuberculous abscesses. In another child, one year old, another bilateral tuberculosis of the thymus, caseated in type, was found. The tracheobronchial glands were heavily involved. The microscopical examination, showed that the thymus in places had undergone connective tissue formation, that the congestion was very marked, and that Hassal's corpuscles had almost entirely disappeared. In another child, ten years old, the left thymus was almost entirely caseous and the center contained a great amount of pus. The right lobe was free from tuberculosis. Microscopical examination of the right lobe showed that the differentiation between the medullary substance had almost entirely disappeared, that the sclerosis was quite advanced in the non-tuberculous portion of the left lobe, while not so marked in the right one. Hassal's corpuscles were very scant in the portions of the thymus involved by the tuberculosis. In a twenty-seven months old child, who died of bronchial pneumonia following whooping cough the thymus was found involved by tuberculosis. The connective tissue was markedly developed; the cells of the thymus were polymorphic in character, and the Hassal's corpuscles were mostly absent. In another child, nine months old, the tracheobronchial glands were tuberculous.



There was at the same time a small cavern in the right lung. The thymus also was caseous. The sclerotic portions showed a marked polymorphism of the cells and a diminution of the Hassal's corpuscles. In all these cases examined, the presence of tubercle bacilli was made certain.

As said before, tuberculosis of the thymus may affect the miliary or the caseous type. In miliary tuberculosis it is not uncommon to find a few small tuberculous nodules throughout the thymic parenchyma. In certain instances the center of these nodules is caseated, and these caseated portions vary in dimension from the size of the head of a pin to that of a hazelnut. The caseated type is the more frequently found. In less frequent instances the caseation may be extended to the whole thymus; in such cases a large cavern, very irregular in surface, is observed. These tuberculous nodules have no special significance except that they are only one phenomenon of a generalized process.

Primary caseous tuberculosis is rare. Secondary caseous tuberculosis is more frequent. It is found in connection with caseous tuberculosis of the mediastinal lymph nodes. Often, however, in very advanced caseation of the mediastinal lymph nodes, one is rather surprised to find the thymus absolutely untouched.

In leukemia and in Hodgkin's disease, the thymus seems to be usually uninvolved, although the mediastinal lymph nodes may be very hyperplastic.

### TUMORS OF THE THYMUS.

Primary tumors of the thymus are most likely not so rare as they would at first seem. Like other organs, we find in the thymus, *benign* and *malignant* tumors.

The word *thymoma* was first intended by Grandhomme, in 1900, to designate the lymphosarcoma of the thymus gland. The coining of the word is a happy one, in so far as it designates the organ involved, but it does not give any information as to the nature of the tumor. Indeed, a thymoma may be benign or it may be malignant. If malignant, it may be sarcomatous, or carcinomatous, or both together. Hence, we ought to say a carcinomatous thymoma, a sarcomatous thymoma, etc.

**Benign Thymomata.**—A *lipoma* has been reported by Wadde, Münchmeyer and Müller.

A *myxoma* was described by Winogradow.

**Fibroma.**—In 1909, Winkler observed a case of atrophic cirrhosis of the thymus in a thirteen-year-old child. The tumor was a large mass, 22½ cms. wide, 9.8 cms. long, and about 2 cms. thick, hard, nodular surface, and attached to the neighboring tissues. The mass was removed by operation after making a partial resection of the sternum. It was

composed of connective tissue, more or less well organized, containing foci of lymphocytes and fatty degeneration. Small, round figures resembling Hassal's corpuscles were observed. Winkler regarded this as a fibroma.

**Dermoid Cysts** are rare. They may be uni- or multilocular and contain hair. No other fetal tissue has been found.

**Cysts.**—Thymic cysts are rather rare. Two great varieties are described: 1. The *ciliated cyst* present in human beings as well as in animals. They are lined with cylindrical, ciliated epithelium and are found in fetus and newborn. They are usually located in the same portion of the gland, namely, in the superior pole and in the cortical substance. That this is not always the case, however, has been proved by Pigache and Bécèle, as shown later.

Remak, in 1855, was the first to notice in cats the existence in the thymus of cysts lined with ciliated epithelium. Watney, in 1883, observed it in dogs; Capobianco, in 1892, in the cat; Tourneux and Verdun, in 1897, in human fetuses; Von Elner, in 1902, Hammar, in 1905, in the cat, dog, chicken and frog. Dustin, in 1909, observed it in the thymus of lizards. In 1896, Nicholas found ciliated cysts not only in the thymus, but also in the parathyroids.

Pigache and Bécèle, in 1911, observed similar cysts in a dog, two rabbits and a mouse. These cysts were nearly always found in the medullary portions of the thymus. They were extremely irregular in character and the cells which constituted their lining wall were in turn cylindrical, cuboidal, or pavementous. These three morphological differentiations of the cells were usually combined in the same cyst. Many of these cells were ciliated, but by no means all of them, and the ciliated ones were disposed in a very irregular way. The lumen of the cyst contained always a mass of cellular detritus showing all stages of degeneration.

In adults, cysts of the thymus are very rare. Hueter, however, reported a very interesting and unique case of a large cystic formation in an adult. The tumor was 76 mm. long and 28 mm. wide. It was polycystic resembling in every respect a bunch of grapes. The tissue between the cysts was absolutely normal and contained a great many Hassal's corpuscles. The connective tissue was more or less marked and sclerotic. In the cyst itself the polypoid arborescences and cholesterin were present. Nothing suggestive of malignancy in these cysts was present. Similar observations have been made in animals.

Hueter observed small thymic cysts in individuals, between eighty and ninety years of age. No syphilis was present. These small cysts were the size of a pea, contained a great deal of cholesterin and were located in a fatty mass supposed to be the thymus. That it was really

so, was revealed by the fact that the microscope showed the typical structure of the thymus.

Chiari thinks that congenital cysts are due to degeneration of Hassal's corpuscles. Eberle thinks that they take their origin in unobliterated segments of the excretory canals of the thymus. Tuve believes that the cysts are of syphilitic origin and are formed by necrosis of parenchyma becoming surrounded by an inflammatory zone which is finally converted into a thick capsule with a few cuboidal epithelium.

Not one of these possibilities only, but all three of them must be regarded as capable of producing cystic tumors.

2. *Congenital Syphilitic Cyst.*—These cysts are lined with a squamous cell epithelium and contain a great deal of more or less degenerated cellular tissue and frequently there is some pus. They are often known as "Dubois Abscesses." (See Syphilis of the Thymus.)

**Malignant Thymomata.**—Malignant tumors of the thymus may be classified in two large groups: those belonging to the family of *sarcomata*, and those belonging to the family of *carcinomata*.

Those most frequently found are the *sarcomata*. They take their origin in the connective tissue of the thymus. The lymphoid cells of the cortical substance are capable, too, of giving rise to sarcoma, hence, the name, *lymphosarcoma*. This is the most common form.

The pure *carcinomata* are more rare, whereas, the mixed tumors are more common. The thymic carcinoma occurs rather in later life, while the *lymphosarcoma* occurs in an earlier period.

There is great confusion in the nomenclature adopted by writers concerning malignant thymomata. The reason is because there is often much difficulty in singling out sharply every variety, the differences between *carcinomata* and *sarcomata* sometimes being very slight. It is not so uncommon to find some authors calling a carcinoma what some others call a sarcoma, and *vice versa*. This confusion is due, according to Ambrosini, to the great polymorphism of the thymic cells, of the lymphocytes, the reticular cells, the giant, plasma and eosinophile cells. Their interrelation produces a histological picture very similar to the one of Hoskin's granuloma, hence, according to Ewing: "The great majority of thymic tumors, and especially of mixed growths, represent infectious granulomata, or particular forms of cell growths on the basis of the infectious granuloma. This, from the etiological point of view, offers a simpler explanation for the great variety of structural forms which thymic tumors present."

The sole criterion that one can accept for the diagnosis of any sort of tumor of supposedly thymic origin is the presence in that tumor of Hassal's corpuscles. In surveying the literature so reported, only a few can be accepted as primary tumors of the thymus. A great many of the

cases reported are probably of thymic origin; the absolute proof that they are really so, namely, the presence of Hassal's corpuscles, is lacking. If, however, polyhedral or giant cells are not present, the probability of the thymic origin of these tumors becomes more certain, because, according to Ertmann, Weigert and Lacquer, these large cells are most likely derived from the reticulum. On the other hand, if it is really true that the reticular cells are epithelial cells (almost everybody seems to admit the fact) then it is very difficult to understand how epithelial cells could give rise to sarcomatous ones.

As a general principle, malignant thymomata of the thymus grow slowly. This, however, is not always the case. Ambrosini saw 5 cases which were fatal in from two to nine months. I saw one fatal in ten months and another in two years.

Their anatomical location will explain why pressure takes place not only upon the trachea, but also upon the esophagus, the base of the heart, the arteries and veins of the mediastinal space, upon the vagus, the recurrent pharyngeal, and the phrenic nerves. In later stages of life, the tumors involve the pleural cavity and the lungs.

Steudener, in 1874, reported a primary sarcoma of the thymus of the hemorrhagic type. The patient, who had always been in good health, previously, died from pneumonia, and the sarcoma was a postmortem finding. It was the size of an apple and surrounded by a very thick connective tissue capsule, soft in consistency, and more or less round in shape. The microscopical examination showed it to be a round-cell sarcoma and the diagnosis of thymic sarcoma was based upon the presence of small cells which were regarded as thymic cells and upon the presence of reticular cells. No Hassal's corpuscles were observed.

In 1878, Oser reported a case of lymphosarcoma of the thymus in a man. The microscopical examination indicated that the tumor was of lymphoid origin. No Hassal's corpuscles were described. Here again the thymic origin is in doubt.

In 1892, Schneider reported a case of *fibrosarcoma* of the thymus without, however, giving absolute proof that the tumor was of thymic origin, as no Hassal's corpuscles were reported. The cells were of the round cell type and the connective tissue was quite marked.

Acker, in 1896, reported a case of sarcoma of the thymus, which, on postmortem, proved to be a large tumor, soft, lobulated, lying in the superior mediastinal space, and involving the trachea and large vessels. Microscopically, the examination proved it to be a large round-cell sarcoma. No mention is made of the presence or absence of Hassal's corpuscles.

In 1896, Gabcke reported a case of spindle-cell sarcoma of the thymus in a twenty-five-year-old woman, who finally died from suffocation.



Here again, we have no indication of the absolute proof of the presence of Hassal's corpuscles.

In 1898, Ertmann reported a large cell sarcoma of the thymus in a man, forty years old. The tumor filled the anterior mediastinum and extended as far upward as the thyroid. No Hassal's corpuscles were found.

In 1901, Hauser reported a case of lymphosarcoma of the thymus in which the undoubtedness of its thymic origin was confirmed by the presence of numerous Hassal's corpuscles.

Weber, in 1901, reported a case of sarcoma of the thymus but no microscopical examination is given.

In 1903, Meggendorfer reported a case of sarcoma of the thymus occurring in a man, forty-seven years old, in whom marked symptoms of myasthenia gravis were present. The patient choked to death. Microscopical examination showed the tumor to be composed of large round-cell sarcoma surrounded by a mass of connective tissue. No Hassal's corpuscles were found.

In 1903, Torri reported a case of myosarcoma of the thymus in a woman, fifty-six years old. The tumor was rather firm, lobulated, occupying the anterior mediastinum. Microscopical examination showed the tumor to be composed of lymphoid cells, small, round-cell sarcoma, and large cells resembling fibromuscular cells. Furthermore, numerous Hassal's corpuscles were present. These fibromuscular cells probably originated from the myoid cells.

Stockert, in 1905, reported a case of lymphosarcoma in the thymus of a man, thirty-six years old. The mass was located in the anterior mediastinum, and extended from the diaphragm to the cervical region. The trachea and esophagus were not at all compressed, although in intimate contact with it. On microscopical examination the tumor proved to be lymphosarcoma of thymic origin. Numerous Hassal's corpuscles were found.

Grawitz, in 1911, reported a case of thymic lymphosarcoma which perforated the heart. No microscopical report is given upon the nature of the case.

Sheen, Griffiths and Scholberg, in 1911, reported 2 cases of sarcoma, 1 occurring in a patient about seven years old and the other in a patient of eighteen years. Postmortem showed that the tumor occupied the position of the thymus, had invaded the sternum, and had caused metastases in the lungs and heart. Death was due to suffocation by pressure on the windpipe. The pathological examination showed that the sarcoma was of the small, round-cell type. The tumor was nodular in surface and had the shape of the thymus. No mention is made by the authors of the presence or absence of Hassal's corpuscles.

In 1912, Simmonds reported 6 cases of malignant tumor of the thymus. Five cases were of sarcomatous type and 1 was carcinomatous. One of the sarcomatous cases had its origin in a dermoid cyst of the thymus. In the sarcomatous thymomata Simmonds was not able to demonstrate the presence of Hassal's corpuscles, while in the carcinomatous, Hassal's corpuscles were present.

In 1920, Holt reported a primary sarcoma of the thymus in a child of six months. At necropsy a sarcomatous thymus weighing 36 grams was found. Metastases were observed in the lymph nodes, spleen, and in the lungs.

In 1920, Foot reported a case of a malignant thymoma in a boy, nine years old. Necropsy revealed a very hard mediastinal tumor, occupying largely the anterior mediastinum and lying just behind the sternum, but not infiltrating the bone. Metastases and lymph nodes were observed. Histologically, the tumor was found to be composed largely of small cells resembling microlymphocytes, but having vesicular nuclei and acidophile cytoplasm.

**Sarcomatous Thymomata.**—Sarcomatous thymomata are generally soft, although some are found showing general fibrosis of the tumor. The surface is usually smooth; in rare cases it is found to be nodular. Local softening of the tumor due to necrosis is not frequently observed. Usually, although at first strictly encapsulated, these tumors in a later stage become adherent to the neighboring tissues, invade the organs and spread throughout the entire mediastinal space and the neck. The lymph nodes first involved are the peribroncheal ones. Metastases are very frequent in the axillary and cervical lymph nodes and occasional metastases are observed in the distant organs, such as the spleen, pancreas, kidneys, liver, adrenals, and finally in the bones and muscles. That sarcomatous thymomata should finally corrode and perforate the sternum is not a characteristic property of theirs. Any malignant tumor of the chest and any large aneurysm of the aorta can do so.

The microscopical picture of the thymic lymphosarcoma, in many instances, does not differ very much from the one of *granuloma malignum*. Sometimes, the only difference between the two conditions is the presence of Hassal's corpuscles.

On close examination, the round cell tumors of the thymus according to Ewing, are found to differ little in structure from the round cell tumors of the lymph nodes. The lymphocytes are few. The chief cells showing mitoses are rather polyhedral in shape, with acidophile cytoplasm, vesicular nuclei, and well developed nucleoli. They often cling to the walls of the numerous small capillaries where they assume a cubical or even cylindrical form. They frequently produce abortive Hassal's corpuscles. Still, according to Ewing, the giant cells are of two main

types: (1) The poor-staining reticular cells with their irregular contour and containing vacuoles and red-cell detritus; (2) the myeloid giant cells with opaque acidophile cytoplasm and many vesicular nuclei. These giant cells do not look like the smaller giant cells of Hodgkin's disease. Increased connective tissue formation is usually present.

The most frequent form of sarcoma found in the thymus is the lymphosarcoma. All other varieties of sarcoma may be, however, encountered, such as the spindle-cell sarcoma, the myosarcoma, the fibrosarcoma, etc.

**Spindle-cell Sarcoma.**—Spindle-cell sarcoma has been encountered; it takes its origin from the connective tissue of the thymus gland. Such a case was reported by Gabcke, in 1896, although he failed to find Hassal's corpuscles.

**Carcinomatous Thymomata.**—In 1890, Letulle described for the first time a pavimentous epithelioma of the thymus.

In 1894, Vermorel, Thiroloix and Ambrosini reported two cases of carcinoma of the thymus.

In 1896, Paviot and Gerest published another case of primary epithelioma of the thymus, and Piery, in 1901 described a tumor which upon microscopical examination proved to be a primary epithelioma of the thymus because thymic tissues and Hassal's corpuscles were present. An interesting fact in connection with this description is that the tumor was observed in a child, one and one-half years old, and that most likely the tumor was of congenital origin, as the parents noticed a growth three months after birth. The tumor, furthermore, was of the polycystic type resembling the polycystic tumor found in the ovary.

In 1902, Eisenstädt reported a case of cancer of the thymus in a young woman, twenty-eight years old. The tumor was very large and filled entirely the anterior mediastinum, was nodular and somewhat elastic. The lungs and trachea were adherent to the tumor and the windpipe was very much compressed. Metastases were present. The microscopical examination revealed the presence of a great many cells, epithelial in character, probably of medullary origin, hence, the diagnosis of carcinoma. No Hassal's corpuscles were present.

In 1907, Thiroloix and R. Debre reported another case of epithelioma of the thymus.

In 1908, Achard and Paiseau reported a case of thymic epithelioma located in the thyroid and having its starting-point there. The epithelium was composed of squamous cells and Hassal's corpuscles were numerous and easily recognized, so that the thymic origin of the tumor could not be doubted.

Rubaschow, in 1911, reported the accidental discovery of a mediastinal tumor which caused no mechanical symptoms whatsoever. The

microscopical examination showed it to be a carcinoma of the small-cell type. No Hassal's corpuscles were demonstrated.

In 1920, Gand and Pidelievre reported a cancer of the thymus in a man, forty years old.

**Carcinoma** of the thymus may be classified as:

1. The *epithelioma* of the Malpighian type.
2. *Medullary carcinoma*.

Classification is made according to the predominating type of cells present in the tumor.

Epitheliomata of the Malpighian type are all characterized by very dense connective tissue containing strings of epithelial cells which resemble very much those seen in the Malpighian layer of the stratum mucosum of the skin. Letulle mentions mucoid degeneration of these cells. Most of the tumors reported contain Hassal's corpuscles, so that their thymic origin cannot be doubted. Most likely, the origin of these epitheliomata is due to branchial inclusion during embryological life. It may be also due to remainders of the thymic ducts. Most likely such tumors may originate from the Hassal's corpuscles themselves which we know are constituted of epithelial cells.

The carcinomatous thymoma takes its origin, most likely, from embryonic restes of the thymopharyngeal duct, or from the reticular cells, or from the Hassal's corpuscles.

**Mixed Malignant Thymomata.**—Not so uncommonly both types of tumors are mixed together, as in the thyroid. They present histologically the characteristics of sarcoma and carcinoma combined.

**Relation of Thymomata to Myasthenia Gravis.**—Oppenheimer, Weigert, Lacquer and Buzzard thought these tumors were associated with myasthenia gravis. In all cases of myasthenia gravis, Mendelbaum and Ceelar found a concomitant growth of the thymus. The same results have been reported by other observers as Burr, Link, Klose, etc. In these cases of myasthenia gravis polynuclear lymphocytes, eosinophiles, plasma and epithelioid cells were found in the skeletal musculature. The true significance of these cells, namely, if they are to be considered as of metastatic origin, or purely of inflammatory origin, is not yet understood.

Bell and Holdstaff who reviewed 250 cases of myasthenia gravis and studied the pathological condition of the thymus in the 28 cases that came to autopsy found the thymus enlarged in every instance.

Of 56 autopsies that have been published since then, the thymus has been found enlarged in 17 and contained a tumor in 10 cases. Hart believes that patients with myasthenia gravis are congenitally predisposed to it. Why they should be so, is not clearly explained. Beside this congenital predisposition, he considers the thymus as a very impor-



tant etiological factor in the production of myasthenia gravis, and furthermore states that removal of the thymus produces cure. He admits, however, that there are cases without thymus hyperplasia.

Jones reports a case of myasthenia gravis in which autopsy following sudden death showed a tumor of the thymus. Microscopically, the tumor was shown to be composed of fetal thymic tissue.

Whatever the relation between myasthenia gravis and thymomata may be, one thing is sure, namely: all thymomata are not followed by myasthenia gravis, and in all cases of myasthenia gravis, thymomata are not always present. That etiological relation exists, if any, between myasthenia gravis and thymic disturbances still remains to be demonstrated.

### STATUS THYMOLYMPHATICUS.

Thymus hyperplasia is not infrequently combined with a concomitant hyperplasia of the entire lymphatic system. In this state the tonsils and adenoids are enlarged; the lymphatic ganglia and their follicles are hyperplastic; the follicles of the base of the tongue are markedly increased; the spleen is larger than normally and the adenoid tissue of the entire lymphatic system is involved. This condition is known as the *status lymphaticus* of Paltauf. When there is a concomitant hyperplasia of the thymus, the condition is then known as *status thymolympathicus*. When the thymus alone is enlarged the condition is called *status thymicus*.

*Status lymphaticus* and *status thymolympathicus* are frequently accompanied by a reduced caliber of the aorta and of the arterial system. Hypoplasia of the adrenals and of the genital apparatus is, too, of common occurrence.

Histologically, the lymph nodes in *status lymphaticus* show enormous increase of the lymphocytes and at the same time of the connective tissue framework. The same process takes place in the genital apparatus, especially in the testicles and the ovaries with the difference that hyperplasia of the parenchyma cells is less marked, while hyperplasia of the connective tissue is markedly increased, thus causing fibrosis of the organs involved. Schridde claims there are two forms of hyperplasia of the thymus: one affecting the cortical and medullary substances in about the same proportion, and the other involving only the medullary substance, the cortical substance being hypoplastic. In this case the reticular cells are large and show signs of active proliferation, while Hassal's corpuscles exhibit the picture of fatty, hyaline, and calcareous degeneration. The first form is practically found only in young children; the second is the more common form.

Lymphatic patients do not stand infections well, especially when

young. Basing his conclusions upon 2500 autopsies of lymphatic patients Bartel found:

56 per cent died between 15 and 25 years of age.  
20 per cent died between 26 and 35 years of age.  
20 per cent died between 36 and 45 years of age.  
4 per cent died between 46 and 65 years of age.

Patients affected with status thymolympaticus are pale, yellowish in color, although, more or less, well nourished. It is often said of them that they have a lymphatic habit, a condition more easily recognized than described. The skin is thick, pasty looking; the hair is poorly developed in men as well as in women, especially the hair of the face, of the genitalia, and of the axillary spaces. It is not uncommon to find lipomata here and there in the body. The skeleton shows some abnormality, too, in length and formation. Bartel, after measuring 30 cadavers of patients who had died from thymolympaticus, found that the length of the body in 10 to 34 per cent of these cadavers was well above the average. Deformity of the bones and persistence and irregularity of the epiphyseal lines are often present. The medulla of the bones is reddish in color; the thyroid is often hyperplastic. The various conditions described as "Paltauf's status thymolympaticus," "Comby's infantile arthritis," "Czerny's exudative diathesis," "Haubner's lymphatism," and "Kryloff's lipomatose type," are most likely only varieties in intensity and shade of the same disease. Such patients have a diminished resistance; they are more vulnerable to bacterial and toxic influences and withstand them a good deal less than others. Their nervous system is impaired; their cardiac function for some reason or other is easily inhibited and death from cardiac paralysis in such cases is frequent.

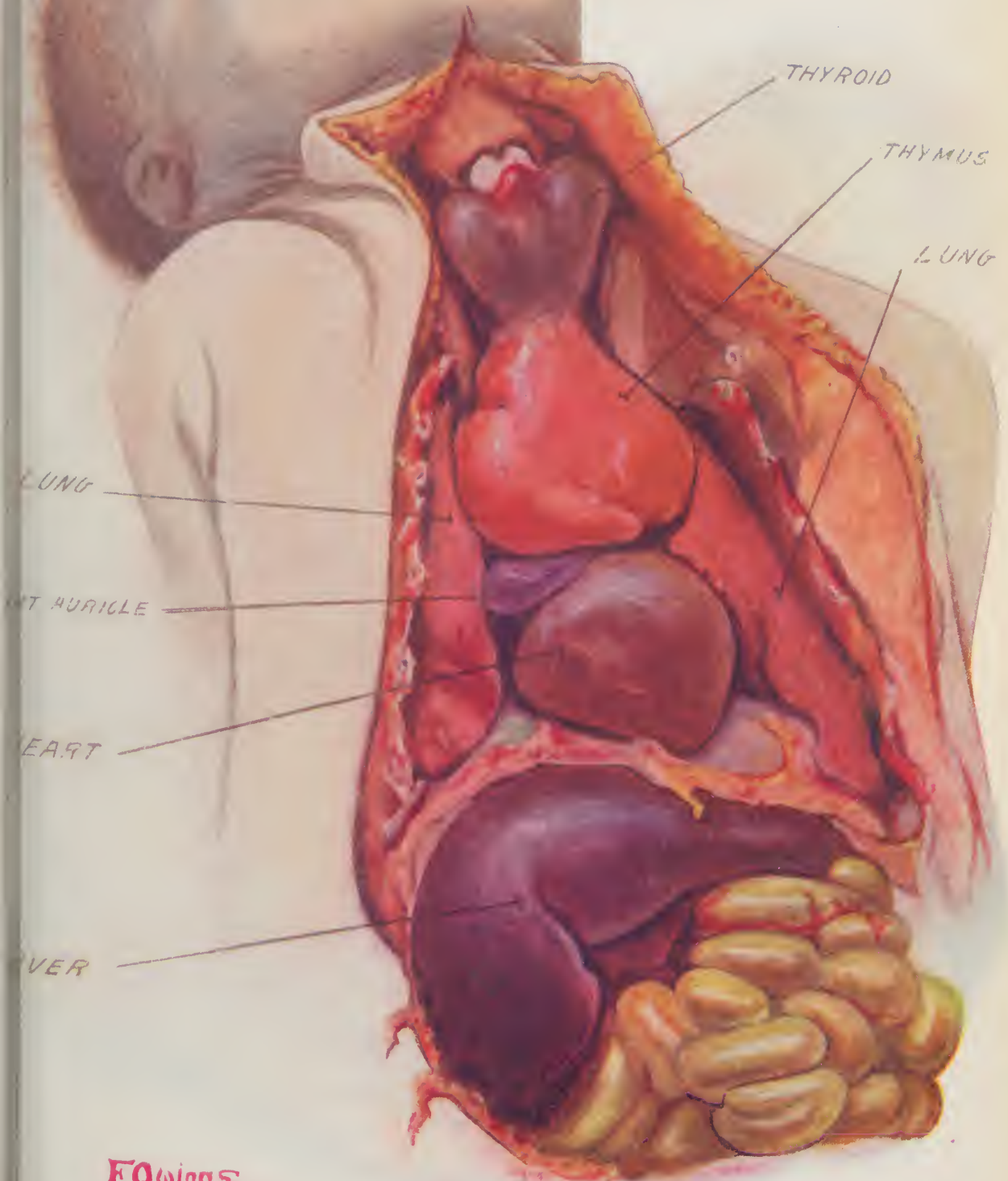
### THYMIC TRACHEOSTENOSIS.

The most striking symptom of thymic hyperplasia is *dyspnea*. This may be characterized by a labored respiration only, or by the most intense choking spells. Between these two extremes all forms of transition are found. Dyspnea may be constant or intermittent, with or without acute paroxysms and between attacks respiration may be normal. There may be a constant persistent respiratory stridor and in extreme dyspnea, an expiratory stridor may also be found, which, however, is less marked. The choking spell may occur without cause, or, for example, when a child cries from pain or anger. Hyperextension of the head or dorsal decubitus exaggerates dyspnea. This would explain why dyspnea is more marked during sleep than during waking hours. The choking spells may last but a few minutes, or a few hours, or a few days, and then

# PLATE XXXV

Newborn Baby Having Died a  
"Thymic Death."

Note the enormous size of the thymus compared with the size of the heart. Note, too, the intimate relation between the thymus and thyroid through the thyrothymic ligament.







respiration will become normal again. In other cases death ensues. In certain cases the child dies at the beginning of the choking spell.

The dyspneic condition begins early, as a rule, in the first weeks or months; diminishes during the second year of life, and is seldom found after this period. This may be due to the fact that the gland normally retrocedes after the second year of life, and that the superior opening of the thorax becomes larger with the growth of the child.

In children the dyspneic symptoms due to thymic hyperplasia may be *acute* or *chronic*.

**Acute Symptoms.**—Certain cases of asphyxia of newborn babies can be explained only by thymic hyperplasia. In such cases the child is born apparently dead, so that it often takes quite a long time to bring it actually back to life. Cyanosis is marked; breathing remains difficult and loud; in many instances the child dies after a few minutes or hours. Postmortem examination shows compression of the windpipe by a hyperplastic thymus. (Plate XXXV) In other instances the child may have been in good health for weeks or months when a most unexpected choking spell occurs. Suddenly, without any apparent cause, or possibly after a few spells of moderate dyspnea, to which likely little attention has been paid, the child throws his head backward and makes intense efforts to get his breath. He rolls his eyes upward, and his face, especially the lips and tongue, becomes cyanotic and swollen. The veins of the neck are congested and a loud stridor is present. The entire accessory respiratory musculature is called into play and a marked “tirage” of the supra- and of the infrasternal fossæ is noticed. Soon, however, everything relaxes and the pupils become widely dilated; cyanosis subsides and is soon replaced by a gray, ash-like color; the lips and tongue become livid. The child is dead. No one has had time fully to realize what was going on. We have all lived through such cases and have all remained stunned and speechless at the sudden and unexpected outcome of the drama.

**Chronic Form of Thymic Hyperplasia.**—Fortunately, all cases do not have such a fulminating character. The choking spells are not all fatal; they subside soon and are replaced by intervals of quiet and easy breathing. Often, however, the respiration remains labored all the way through the attack. These cases are the ones in which an early recognition and prompt surgical treatment will save the patient's life.

In children what might be termed a latent thymus hyperplasia may exist for a longer or a shorter period of time. Such cases, as a rule, do not come under surgical jurisdiction. They are seen by the family physician who finds that the child is in poor general condition and suffering from some vague respiratory disturbances. The physician may, or may not, connect these symptoms with thymus hyperplasia, but even if he makes the correct diagnosis, the parents will likely never consider an

operation necessary until more decided dyspneic symptoms are present. But, unfortunately, sudden death is sometimes the first symptom which reveals the latent form of the thymus hyperplasia and in many instances this unsuspected condition is revealed only at autopsy. Today, however, since we know a little more of the pathological condition, I believe that this fulminating form of death due to thymus hyperplasia without any prodromic symptoms is rare. As a rule, the learned physician will find in the history of these cases a few symptoms which, if well interpreted, will arouse at least a suspicion of a hyperplastic thymus. As in Bright's disease, *e. g.*, so there are in thymus hyperplasia, too, some minor symptoms which will lead the physician to a correct diagnosis. But it is just because such symptoms have not been carefully observed that the diagnosis of thymic hyperplasia is at times not made. As a result the child may be found dead in his bed and autopsy would then show a large thymus compressing the windpipe.

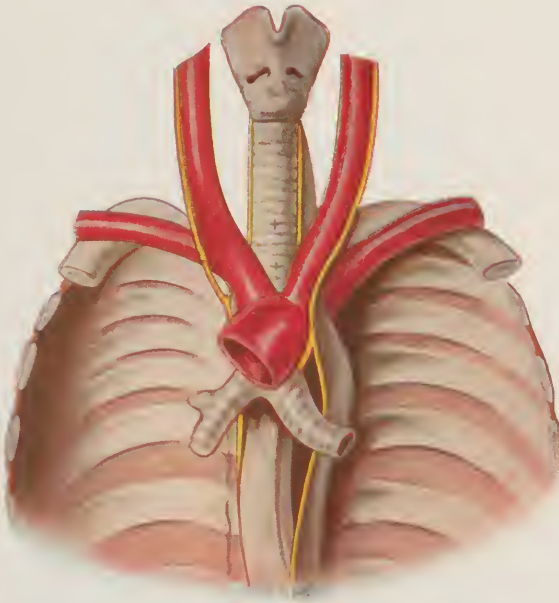
**Explanation of the Choking Spells and of Thymic Death.**—How are we to explain the pathogeny of these choking spells? Pressure may take place at two points:

1. At the superior opening of the thorax.
2. In the thorax.

**Pressure at the Superior Opening of the Thorax.**—We know that in young infants the anteroposterior diameter of the superior opening of the thorax is quite small and that it does not exceed 2 or 3 cm. Because of the relation of the thymus to the thyroid, with which it is connected by the thyrothymic ligament, the thymus will follow the up-and-down movements of the windpipe and larynx, during the various acts of swallowing, coughing and hyperextension of the head, etc. A finger placed behind the episternal notch feels the impact of the rising thymus, consequently, the thymus when hyperplastic comes up like a wedge between the spinal column and the manubrium sterni (Fig. 100). There it is caught and constricted at the superior opening of the thorax, the so-called "critical space of Grawitz." Inasmuch as the bony ring which forms the superior opening of the thorax is not elastic, the organ which it contains must necessarily undergo compression, and since the trachea lies immediately below the thymus, it is the first to be compressed, hence, the choking spells (Fig. 100).

If the superior opening of the thorax cannot increase in diameter, it can, on the other hand, diminish as, for instance, in the hyperextension of the head. In such cases the vertebræ are projected forward and in so doing diminish the anteroposterior diameter of the superior opening of the thorax, hence, the further cause of dyspnea (Fig. 100). This would explain why in certain cases death has followed exaggerated hyperextension of the head.

PLATE XXXVI



The relation of the innominate of the common carotid and aorta to the vagus and inferior laryngeal nerves. It will be easily seen how a tumor compressing and displacing these large vessels will put the inferior laryngeal nerve on the stretch, thus causing closure of the glottis and choking spell. The figure shows, too, where compression on the windpipe by the thymus will take place.





With young children flattening of the windpipe will be so much the more apt to occur, since in them the cartilaginous rings of the trachea are not fully developed.



FIG. 100.—Showing how the thymus during hyperextension of the head or coughing comes up like a wedge and is caught at the superior opening of the thorax, thus compressing the trachea.

**Pressure in the Thorax.**—Another place at which compression of the windpipe may take place, especially in adults, is the point situated between the innominate artery and the left common carotid and the cross of the aorta. (Plate XXXVI.) This compression is not confined to one ring of the trachea alone, but extends over a certain portion of it. This is easily understood when we consider the anatomical relations of

the thymus to the trachea in that region. Since the thymus presses upon the anterior surface of the trachea in the space between the left common carotid and the innominate artery, and since the trachea lies in front of the spinal column, then in cases of sudden enlargement of the thymus, being itself compressed between the spinal column and the sternum, it must obviously exert compression upon the trachea. (Fig. 101.)

The first form of compression which takes place at the superior opening of the thorax is found mostly in children, while the second, or thoracic form, which takes place as above mentioned, between the innominate artery and the left common carotid, is found mostly in adults.

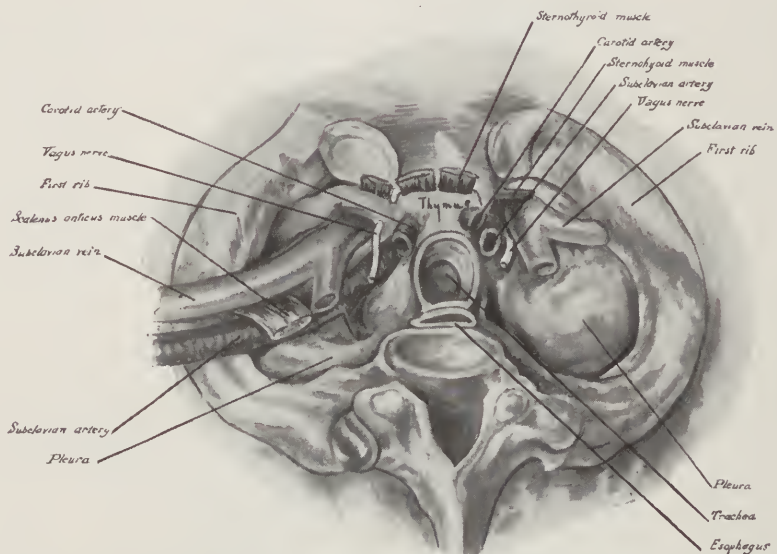


FIG. 101.—Superior opening of the thorax viewed from above in order to show the anatomical relations of the thymus with the other organs enclosed in "bony ring."

**Spasm of the Glottis.**—Inasmuch as a hyperplastic thymus compresses the large vessels, namely, the aorta and the innominate trunk, and as we know the inferior laryngeal nerve winds around these vessels, it will be easily understood that these nerves might become stretched by the displacement of these bloodvessels because of the hyperplastic thymus. (Plate XXXV.) We have already seen that irritation or stretching of the inferior laryngeal nerves causes spasm of the glottis, despite the fact that dilators as well as constrictors of the glottis are supplied by the same nerve, the inferior laryngeal nerve. The reason lies in the fact that the constrictors of the glottis, being stronger than the dilators, induce irritation of the inferior laryngeal nerve by stretching, which must cause a spasmodic contraction instead of a dilatation, and

consequently a spasm of the glottis. In such cases tracheotomy would save the patient.

In other cases, I believe that direct pressure on the base of the heart and consequently on the heart ganglia may be the cause of death.

In many instances, however, thymic hyperplasia, whether accompanied or not by status lymphaticus, does not interfere mechanically with the trachea, yet death sometimes takes place most unexpectedly and suddenly. I have in mind those cases of sudden death which take place during some intense nervous excitement such as coitus, etc.; those just before or during an anesthesia, and those following a cold bath, etc. In this respect Recklinghausen's case is an extremely interesting one. It was that of a boy who had fallen from a boat into a river, but was rescued at once before he had time to swallow any water, nevertheless when he was taken out he was dead.

In all these above-mentioned cases the only pathological finding was a thymic hyperplasia accompanied or not by a status lymphaticus, but compression of the windpipe was not present. What then is the explanation of such sudden death? Of course, here everything is hypothesis. The fatal issue in some cases may be explained by the sudden swelling of the thymus, due to some exertion such as crying, or to some interference with circulation. Possibly, in other cases, the pressure over the basis of the heart and especially over the cardiac ganglia, may have caused a sudden inhibition of the cardiac system; possibly, too, in certain vulnerable individuals with a nervous system in constant unstable equilibrium, the shock from the peripheral origin as was experienced by falling into cold water, for instance, was such as to totally inhibit the central nervous system. Possibly, too, the laryngotracheal reflex caused by the first few inhalations of the anesthetic agent was powerful enough to inhibit an already unstable cardiac system.

Simmers concludes that sudden death in status lymphaticus may be brought about in two different ways. The first and most frequent cause is in the nature of an anaphylactic reaction due to sensitization of the body by a specific nucleoprotein formed in the lymph nodes as the result of necrosis of numerous germinal follicles. Before the so-called anaphylactic incubation period has expired, the tissues are again subjected to the action of the same protein formed in the same type of tissue in response to apparently trivial injury, and in this way the anaphylactic reaction is completed. A second cause of sudden death in status lymphaticus is found in the form of a spontaneous rupture of a hypoplastic cerebral vessel following an apparently trivial injury; the deficiency in the vessel wall is not noticeable in the muscular coat.

Most likely, however, in many instances the explanation must be an entirely different one, and we shall hold the solution of the problem only

when the problem of internal secretions shall have been solved. As stated before, every organ most likely contains several lipoids, each one possessing a different physiological property; the thymus and probably the lymphatic apparatus do not escape this rule. In marked cases of status thymolymphaticus a concomitant hypoplasia of the chromaffine system, especially of the suprarenal bodies, seems often to be present, hence the supposition of Wiesel that, because the secretion of the suprarenal bodies is insufficient there is not enough adrenin output to entertain a normal and constant excitation of the sympathetic system which is an excitatory system; consequently since the normal equilibrium between the sympathetic and the vagus is disturbed, the vagal inhibitory system takes the upper hand. According to Wiesel, these views are not altogether purely hypothetical, inasmuch as Neusser, Eppinger and Hesse claim that the thymic hormone is antagonistic to adrenin and is vagotonic. Such belief as this is strengthened by the experimental claim that after extirpation of the thymus there is a marked hyperplasia of the cortical portion of the suprarenal bodies. Furthermore, such individuals with status lymphaticus must be regarded as vagotonic; they perspire freely; their respiratory rhythm is easily affected; their blood-pressure is below normal and their arterial system is hypotonic.

We must bear in mind, however, that the vagotonic theory has been assailed by competent physiologists, as R. G. Hoskins, Swale Vincent, etc., who, it is true without disproving it, claim that it is based on purely speculative facts.

Tracy believes that thymus death is due to a superabundance in the blood stream of thymic hormone or "Hormone X" and to an insufficiency of the adrenals. Noël Paton advances the view that thymus death is due to a polyglandular syndrome; in his judgment there is a diminution or absence of the secretion of these organs, and because of an imperfect development death occurs more easily than it otherwise would. McNeil believes that thymus death is due to anaphylactic phenomena occurring in exaggerated forms. Wooley and others think that thymus death is due to hyperthymization. None of these views has been fully substantiated.

**Does Tracheostenosis Really Exist?**—Among some writers there seems to be a tendency to interpret Hammar's publication of 1916 as meaning that death, due to thymic compression upon the trachea, is very much to be doubted. Surely, such conclusions are exaggerated, and cannot be a true representation of Hammar's views upon the subject. Certain it is that every sudden death cannot be attributed to the thymus, and certain, too, that every thymic death cannot be regarded as due to mechanical compression of the windpipe. The reader needs only to refer to the preceding chapter to be convinced of that fact. Nevertheless, cases remain where death is unquestionably due to tracheostenosis.



It would be interesting to know how much actual pressure is necessary to bring about the absolute occlusion of the windpipe in a living subject. Scheele says that a pressure of 750 to 1000 grams is necessary to occlude the windpipe of an adult. Tamassi obtained a complete occlusion with 160 grams and a diminution of the lumen with 125 grams. Kasarinhoff found that 160 grams were necessary to occlude the windpipe and 60 grams to diminish the lumen. Gudobin found that 230 to 260 grams were necessary to occlude the windpipe in the newborn; 700 grams for the windpipe of a one-year old child, and 1000 grams for a five-year-old child. Von Sury found that in young children a pressure of 100 grams made hardly any impression upon the windpipe, and that 200 to 250 grams reduced the lumen of the windpipe but did not occlude it.

As interesting as these figures may be, they do not represent the true conditions of life. They ignore the active and passive congestions that can take place in the mucous membrane of the trachea and the surrounding organs; the normal adhesions of the thymus with the pericardium, with the large bloodvessels, and with the windpipe; they ignore, too, the variations in the diameter of the superior opening of the thorax. They do not, as Klose justly says, take into consideration the atrophying effect a chronic compression of the thymus may have upon the windpipe. In short, they do not take into consideration the real physiological and pathological conditions of the thymus.

For one who has seen cases of death where the typical mechanical disturbances due to respiration were present; who has seen these same cases come to postmortem and show, not only thymus hyperplasia but also present, in cross-sections, an unmistakable flattening of the windpipe accompanied with marked congestion of the mucous membrane, the cause of death can be but *tracheostenosis*. Furthermore, for one who has seen cases with marked mechanical respiratory disturbances and who has performed thymectomy and observed that soon after these the mechanical disturbances disappear, there can be but one cause for the disturbances, namely, *tracheostenosis*. I have in mind, for instance, the case of a young boy, seventeen years old, who had been suffering from a labored respiration and choking spells for many months. Physical examination and x-ray pointed toward thymic hyperplasia as the sole cause of the whole syndrome. Partial bilateral resection of the thymus was performed. As soon as the operation was finished respiration became normal and has remained so ever since. Seven years have elapsed since then and the boy is still in perfect health.

**Diagnosis of Thymus Hyperplasia.**—No matter what the accepted explanation may prove to be, all our efforts should be directed toward detecting the presence of thymus hyperplasia whether accompanied or not by status lymphaticus. In children, the diagnosis is, as a rule, easy.

Percussion over the manubrium sterni reveals a dulness, which, in cases of marked hyperplasia, overlaps on each side the ribs and cartilages (Fig. 102). Auscultation over that region reveals a prolonged expiration tubular in character. A finger placed above the episternal notch may be able to feel the impact of the rising thymus during deglutition, coughing, etc. But the most certain way to detect thymic hyperplasia in children is given by the *x*-ray (Fig. 103). The shadow, its form and location are, so to speak, pathognomonic and the diagnosis may be made with certainty. In adults, however, the diagnosis becomes more difficult. The



FIG. 102

dulness may be present, but may be absent, too. The shadow of the mediastinal space may often be typical, and allow a diagnosis, yet sometimes great difficulties are encountered in deciding whether we have to deal with thymic hyperplasia or not. One of my cases will illustrate this condition very well. My clinical examination did not reveal any symptoms pointing toward thymic hyperplasia, consequently, I decided clinically that a thymus was not present, yet the *x*-ray showed a shadow with the characteristics of thymic hyperplasia. I consequently concluded that I had been misled by my clinical findings and that my conclusions

were erroneous. However, not long after, postmortem showed that no thymic enlargement was present.

**X-ray Characteristics of Thymus Hyperplasia.**—Normally, on a skiagram of an adult, the mediastinal space measures 2.5 cms. to 3.5 cms. under the arch of the aorta; from 3 to 3.5 cms. at the arch of the aorta, and from 5 to 6 cms. at the conus arteriosus. The shadow of this

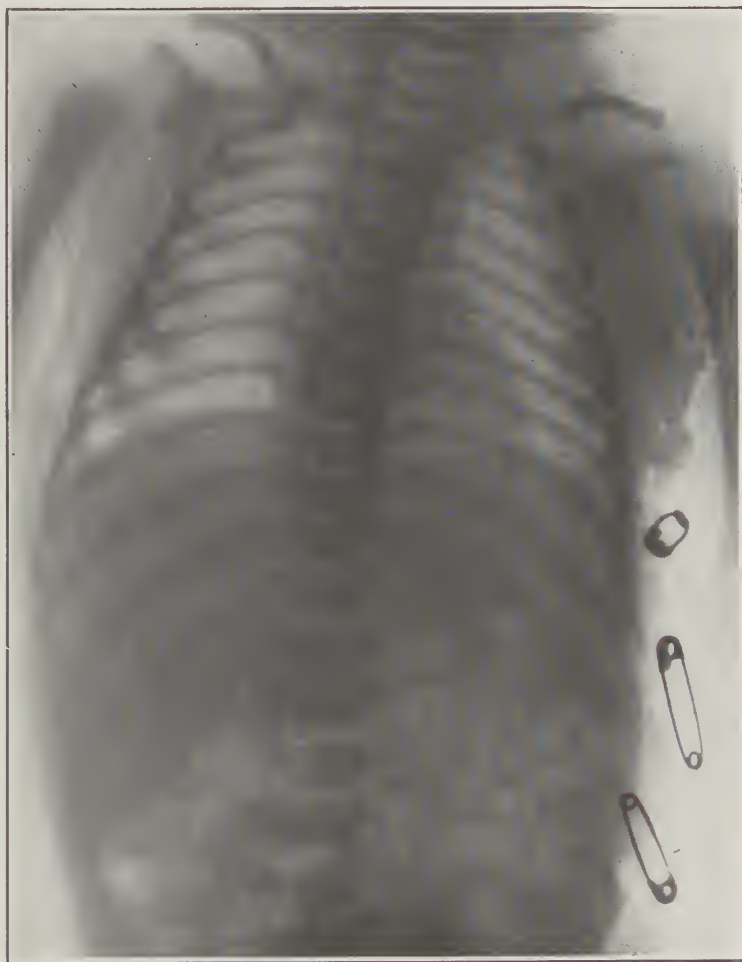


FIG. 103

region is dark, opaque, regularly distributed, and has definite limits. But in thymus hyperplasia there is another shadow which overlaps laterally this mediastinal shadow. This shadow may be found over one lobe more than the other, or over both in the same proportions. Again, the shadow may be more or less triangular in shape, and may extend

upward from the region of the auricle in a straight line, or may follow to some extent the contour of the mediastinal shadow. Sometimes, the region of one or both auricles may bulge out as if the auricles were over-distended, thus forming an angle between the ventricle and the auricle. In that case the base of the heart is enlarged and the enlargement is not in proportion to the size of the heart. The thymic shadow in some cases is superimposed on the base of the heart like a cap which fits right over the base of the heart. The character of this shadow differs extremely from the cardiac and mediastinal shadow. It is thin, transparent, soft, and regularly distributed and the edges are, as a rule, sharply limited and linear.

**Differential Diagnosis of Thymic Hyperplasia.**—It would be a mistake to believe that thymus enlargement is the only cause which may give rise to a congenital stridor and respiratory trouble. Such conditions may also be found with malformations of the vestibulum of the larynx, with tracheobronchial glands and with adenoids. An accurate differential diagnosis must be made between the different forms of stridor.

The *congenital vestibular stridor* is seen after birth. It is entirely inspiratory and is not found on expiration, except in rare cases. Cyanosis is present, too, but the stridor and dyspneic symptoms disappear with intubation of the larynx, which is not the case for thymic dyspnea in children. The laryngoscopic examination when possible and the autopsy when obtainable will show that this stridor is due to a malformation of the superior opening of the larynx. The epiglottis has a "gutter" or "beak-like" form, and is folded in the middle line. The plicæ aryepiglotticæ of both sides come in contact, one with the other; they are pulled down over the opening of the larynx and so diminish the orifice, hence, dyspnea and stridor.

Stridor due to *tracheobronchial* glands is found mostly on expiration, and like the voice has a bitonal character. Furthermore, the thymic stridor is often congenital, whereas, the tracheobronchial stridor is acquired and has usually a long history of coughing, etc., behind it. Percussion and radioscopy will reveal entirely different findings.

*Adenoids.*—In adenoids there may be difficult and labored breathing which may be more noticeable during sleep, but in such cases diagnosis will be easy.

Thymic stenosis should not be mistaken for a *retrovertebral abscess* or for an *acute laryngitis*.

In *laryngismus stridulus* the period of apnea is usually short; respiration soon begins again. *During the intervals respiration is usually normal*, whereas, in thymic tracheostenosis respiration remains more or less embarrassed all the way through. *Laryngismus stridulus* is nearly



always one of the manifestations of infantile tetany and is usually accompanied by other stigmata, such as Erl's, Chvostek's and Trousseau's symptoms. It is more prevalent in spring and autumn than at any other time of the year.

Inasmuch as a hyperplastic thymus may come in contact with and compress the right and left auricle and ventricle, the superior vena cava, the aorta, the innominates, and the left common carotid, cyanotic symptoms, characterized by distention of the veins of the neck, by puffiness of both supraclavicular spaces, and by cyanosis of the face, and distention of the large fontanelle may be present. During the paroxysms these symptoms become extremely marked. The veins of the neck are much distended and the fontanelles protrude; the face is puffed and the child is in a semicomatose condition. The heart beats violently, or in certain cases stops altogether. When the paroxysm is over the symptoms retrocede, but in other cases death ensues. Autopsy shows that compression of the right ventricle and of the superior vena cava and aorta is very marked. In such cases the dyspneic symptoms are of secondary importance. The vascular symptoms dominate the scene and extreme repletion of the face and neck, distention of the large fontanelle, and the tendency to collapse, will differentiate this form of cyanosis from that due to malformation of the heart. In blue babies the cyanotic condition of the patient is uniformly distributed and persistent.

**Relation of Thymic Hyperplasia to Thyrotoxicosis.**—For a long time the presence of thymic hyperplasia in connection with Basedow's disease was thought to be merely a coincidence and usually a matter of accidental autopsy findings, but in late years, however, the trend of opinion has changed considerably and the facts have become so numerous and so convincing that it is no longer possible to doubt that some sort of relation exists between thymic hyperplasia and thyrotoxicosis. Thus Moebius, in 1818, reported a large thymus in a case of severe thyrotoxic goiter. In 1858, recording the autopsy findings of a case of "big goiter" with cardiac disturbances, Markham noticed that the thymus was markedly hyperplastic. In 1889, Moseler observed a very large thymus in a case of thyrotoxic goiter death. Bonnet, in 1899, reported 28 cases and Thorbecke, in 1905, added 35 more cases to the list with similar findings. Thorbecke was of the opinion that thymus hyperplasia had no influence upon the histological picture of the thyrotoxic goiter, although there undoubtedly existed in his judgment, a direct relation between thyrotoxic goiter and thymus hyperplasia. Gierke claimed that 55 per cent of the patients dying soon after thyroidectomy had been performed have an enlarged thymus, but that otherwise the frequency of thymus hyperplasia in thyrotoxic patients is not as great as

has been claimed. This author thinks that possibly the thyroid and the thymus are in direct chemical relation and that the increased thymic secretion directly affects the heart and brain. On the other hand, Rössle believed there is no direct relation between thyrotoxicosis and thymic hyperplasia. He did not accept Gierke's theory of antagonism between the thyroid and thymus but he was rather inclined to believe that the two organs have a vicarious function.

Von Hanseman, in 1905, found that 75 per cent of the thyrotoxic cases coming to autopsy had a marked thymic hyperplasia. (Note that Von Hanseman's conclusions are based upon autopsy findings only, a fact that adds considerable strength to his statement.)

In 1906, Kocher reported a series of 59 cases in which 49 showed increased hyperplasia of the cervical lymph nodes. In his judgment, this hyperplasia of the lymphoid system was due to direct irritation from the thyroid secretion and there is no relation between thyrotoxicosis and thymus hyperplasia.

In 1908, Rehn reported a series of 360 cases of thyrotoxic goiters with 42 deaths, six of these being due to thymic hyperplasia. In his judgment the cause of death was purely a mechanical one; there occurred swelling of the thymus causing pressure upon the trachea and the blood-vessels.

In 1908, Cappelle reported 60 cases of thyrotoxic goiter in which 79 per cent of the patients had thymus hyperplasia. Of these cases 19 died of intercurrent diseases, of which 44 per cent had enlarged thymus; 17 cases died of thyrotoxicosis itself of which 82 per cent had enlarged thymus. This statement, coming at a time when Kocher and Mayo were trying to popularize thyroidectomy was not made without causing a startling sensation in the surgical world. In Cappelle's judgment the thymus hyperplasia is secondary to the thyrotoxic condition and the presence of thymus hyperplasia is a contraindication to operation.

Gaupner, in 1910, reported 3 cases of thyrotoxicosis where thymus hyperplasia was present, and Gebele found it in 4 out of 5 cases. Gebele thought that the thymus plays the part of a detoxicating organ and that the thyroid and thymus have a vicarious function. He regarded thymic hyperplasia as a contraindication for thyroidectomy.

In 1911, Garré, after having obtained brilliant results from thymectomy combined with thyroidectomy, namely, unexpected and rapid amelioration of the cardiac function, return to normal of the blood picture, and increase in flesh, admitted that there is a direct relation between the thyroid and thymus in thyrotoxicosis and believed that thymus hyperplasia must be considered as an aggravating factor. He based his conclusion, not only upon his personal clinical experience, but also upon the experiments of Bayer, who by injecting into the peri-

toneal cavity, juice obtained from thyrotoxic goiters and hyperplastic thymi obtained the typical blood changes observed in thyrotoxicosis. Furthermore, he based his conclusions upon Bircher's experiments, and upon the histological pictures of thyrotoxic goiters where thymectomy had been previously performed, showing regressive changes taking place in the thyroid.

Schultze reported 54 thyrotoxic cases with 9 deaths following thyroidectomy. Eight of these cases showed marked thymic hyperplasia. Cappelle and Bayer came to regard thymus hyperplasia as a very severe complication in thyrotoxicosis and claimed that the thymus and thyroid mutually increase their nocive influences. In their judgment, a thymogene autointoxication takes place and finally causes a cardiac death which is entirely different from the death seen in children. Like Garré, they based their opinion upon Bircher's and upon Kostlivy's experiments, the latter claiming that thyrotoxic goiter exerts an influence upon the sympathetic and the autonomous systems.

In 1911, Simmonds shared Kocher's view, namely, that enlargement of the lymphoid apparatus in the region of the thyroid is directly caused by the thyroid secretion, and that hyperplasia of the remainder of the lymphoid system as the spleen, lymphoid apparatus of the intestine, and thymus are only a part of the status thymolymphaticus.

In 1911, Baruch found thymus hyperplasia in conjunction with thyrotoxicosis in 4 out of 10 autopsies. Likewise Hildebrand, in 2 out of 5; Küttner, in 2 out of 11; Von Eiselsberg, in 4 out of 6; Matti, in 7 out of 10; and Von Baily in 4 out of 8 autopsies.

In 1911, Kocher considering the relation between thymus hyperplasia and thyrotoxicosis, and basing his conclusions upon Falta's theory, believed that the thymus secretion exerts an influence upon the autonomous system by causing an irritation of that system and consequently affecting the lymphoid apparatus, spleen and thymus.

In 1912, Bircher claimed to have produced on five dogs a typical Basedow by intraperitoneal implantation of fresh hyperplastic thymus taken from non-toxic cases. In one case the thymus came from a patient in whom the gland caused stenosis of the trachea; in other cases it came from patients who died following operation. He never used the thymus of a Basedow patient. In one case he implanted a fresh piece of thymus the size of the palm of the hand and 1 cm. thick in the omentum of a dog. The thymus was taken from an endemic cretin who had tracheal stenosis. The dog showed the first symptoms within twenty-four hours. He was very much excited, ran around in his cage like a mad dog; would scarcely eat; and had an intense thirst. In four days exophthalmos appeared and reached its maximum on the twentieth day, when it gradually began to subside; after five months it had all gone. Three days after the implan-



tation tachycardia started, reaching 180; the paws showed a fine tremor which sometimes extended over the whole body. Five weeks later a goiter could be palpated. At the end of the first week lymphocytosis was present, but it lasted only a short time. The tachycardia was, marked during three months, but later it became noticeable only when the dog was excited. There was no doubt in Bircher's mind that the dog had an acute Basedow caused by the implantation of the thymus gland.

Crotti reported in 1912 a similar observation. He injected in the peritoneal cavity of a dog 15 grams of a thymus removed at the post-mortem of a Basedow patient. Fourteen hours later he noticed nervousness, intense general tremor, brilliancy and slight protrusion of the eyes, increased pulse-rate, slightly increased temperature and loss of appetite. This condition lasted three days and then disappeared. In another dog, however, where he injected 110 grams of thymus, taken from another patient, no symptoms of Basedow appeared. Experiments with implantation of normal thymus gland gave no results.

Klose, in 1912, claimed that there is no thyrotoxic goiter without thymus enlargement. Even the fact that thyrotoxic cases are found where there is no thymus enlargement does not affect his opinion on the subject. He claims that cases where thymic hyperplasia fails to be present, are the very acute ones and of long standing, which have undergone cachexia, and that before one is within his right to assert that thymus hyperplasia is absent, Klose, furthermore claims that seriated histological examinations of the thyroid should be made and of the neighboring organs of the neck so as to eliminate the possibility of a hyperplastic thymus tissue in the thyroid itself, or in the neighboring cervical organs, inasmuch as he has observed a case of thyrotoxic goiter accompanied by a marked hyperplastic thymus IV located within the thyroid itself. In Klose's opinion the thymus and the thyroid are vicarious organs. To substantiate his views he reported the case of a fifty-two year-old woman with sarcoma of the thymus. The patient presented all the symptoms of Basedow's disease, and hemithyroidectomy was performed which produced no benefit. The patient died from the operation for sarcoma. In Klose's judgment the thyrotoxic symptoms were of thymic origin.

Sahli also operated upon a case of sarcoma which presented all the symptoms of Basedow's disease.

Matti, in the same year, accepted Klose's views. He collected out of the literature 133 cases and found that in patients who died from operation 76.5 per cent of them had thymic hyperplasia. In no other condition as in simple and thyrotoxic goiter do we find such frequency of thymic hyperplasia. Matti found that after thymectomy the thyroid increases in size and shows the typical histological picture of thyrotoxic



goiter, namely, diminution of colloid, increase of the epithelium, etc. Von Hanseman, Virchow, Glück, Wiesel, Nettel, Kauffmann, Rössle, Hart and others report the same findings, namely, concomitant thymic hyperplasia with simple goiter.

In 1914, A. Kocher reported that there is a hyperplasia of the thymus in about 45 to 50 per cent of the cases. This hyperplasia is much more frequent in young thyrotoxic patients than in older ones. The age when thymus hyperplasia is most frequent does not coincide with that when thyroid diseases are most frequent. There may be as great an increase in the size of the thymus without thyrotoxicosis. Histologically, there is no difference between juvenile hyperplasia of the thymus and that of Graves's disease. In most cases the hyperplasia of the thymus existed prior to the outbreak of thyrotoxicosis, and so, in his judgment, could not be the direct cause of the latter condition. It is apt to increase after the development of Graves's disease. That may be due to hyperplasia of the adrenal cortex. Kocher claimed that after partial thyroidectomy the thymus spontaneously retrocedes in most cases and that thymic hyperplasia is not a factor of danger in thyroidectomy.

Ochsner, in 1916, reported that he had not been able to make out any enlarged thymus as an accompaniment of hyperthyroidism. He had not been able to outline the thymus gland in his thyroid cases, although the *x*-ray plates had shown frequently that hyperthyroidism was accompanied with enlargement of the thymus gland.

MacKenzie, in 1916, stated that during the past thirty-six years there had been exactly 36 postmortem examinations at St. Thomas's Hospital, London, on cases of exophthalmic goiter. The presence of the thymus was noted in 26 cases, and it was described as greatly enlarged in 6; large or hypertrophied in 16, and persistent but not large in 4.

Melchior, in 1917, although finding enlarged thymus in 75.5 per cent of the thyrotoxic patients, claimed that the thymus plays no part in causing postoperative death in thyrotoxicosis. The prognosis of the operation is much worse with a small thymus than with a large one. In Von Haberer's opinion the severest thymotoxic symptoms may be caused by fragments of thymus so small as to be unrecognizable by the naked eye.

Von Haberer claims that there are cases of Graves's disease in which the thyroid is small; the thymus, however, being very large. In these cases complete recovery is observed after resection of the thymus. He operated in 40 cases this way and never observed a relapse.

Jaboulay lost one patient with thymic hyperplasia after resection of the sympathetic nerve, which operation he performs in all his thyrotoxic goiter cases.

In 1914, Simmonds reported the results of his examination of thymi

in Basedow's disease. In 34 cases he found a large thymic hyperplasia; in 9 cases, the thymus was normal.

In 1920, Nordmann found that in 11 fatal cases of thyroidectomy there was found a persistent and enlarged thymus in every case.

Crotti in his last series of 500 thyroidectomies for goiters of all denominations, in which he began to make a systematic search for thymus hyperplasia by exploring the upper mediastinal space before closing the wound, had occasion to perform 75 thymectomies. These 500 cases include thyrotoxic, non-toxic, as well as malignant goiters. The greatest majority of thymic hyperplasia found were in thyrotoxic cases. None was observed in malignant goiters except in one instance, that of a man above fifty years old, who had had a simple colloid goiter of long standing. Suddenly this goiter began to grow rapidly and become hard. The dominating feature of the case, however, was the accompaniment of a marked thyrotoxic condition plus exophthalmos. The beginning of malignant degeneration was overlooked by his attending physician and consequently much time was lost in treating the patient medically for his thyrotoxicosis. When finally referred to me for operation, the case had become inoperable and the patient died a few days after. Beside an inoperable adenocarcinoma developed in the lower right lobe of the thyroid, postmortem showed a marked thymus hyperplasia.

The interesting feature observed in thymic hyperplasia accompanying thyrotoxicosis is that, contrary to what is observed, in the thyroid, the left thymus is nearly always much larger than the right thymus.

*The weight of the thymus in thyrotoxicosis* varies greatly but is usually very much above the normal, the average weight in normal adults being about 8 grams.

	Found.	Grams.
Soupault	" . . . . .	69
Lejars	" . . . . .	69
Schlaffer	" . . . . .	80
Rautmann	" . . . . .	90
Ghierka	" . . . . .	97
Crotti	" . . . . .	100
Pettavel	" . . . . .	110
Gebele	" . . . . .	130
Crotti	" . . . . .	170
Stordeur and Francois	" . . . . .	250

The significance of these weights is that much the more striking because it would seem that in thyrotoxicosis the thymus ought to undergo a much more rapid involution than in any other condition, had it not a direct bearing upon that very condition itself. Indeed, we know that in such states where metabolism is greatly increased and nutritional disturbances are very accentuated, the thymus undergoes a marked involu-

tion, yet, in thyrotoxicosis where usually the loss of tissues is so great, we have just the opposite; instead of involution we have hyperplasia. We must bear in mind, too, that thymic hyperplasia does not accompany only thyrotoxic goiter, but that it may be found in simple goiter also, as shown by the autopsies of Sir Astley Cooper, Glück, Melchior, Von Hansemann, and many others including myself.

*Thus, it seems that there is between thyrotoxicosis and thymic hyperplasia not an accidental but a direct reciprocal relation. The same seems to be true for thymus and simple goiter.* Remarkable, and somewhat disconcerting, is the fact that thymus hyperplasia is much less apt to be found in very severe and protracted cases of Graves's disease than in the earlier forms.

### WHAT IS THE SIGNIFICANCE OF THIS THYMIC HYPERPLASIA?

Is it a primary or is it a secondary disturbance? In other words, does the thymic hyperplasia cause thyrotoxicosis with its concomitant thyroid hyperplasia, or does thyrotoxicosis cause thymic hypertrophy? This question has been answered differently and the answer has mostly depended upon the conception one has had of the histological nature and of the physiological function of the thymus. Those who consider the thymus simply as a lymphoid organ see in the thymic hyperplasia only a hypertrophy of the whole lymphoid system in response to an irritant of some sort. On the other hand, those who are rather inclined to regard the thymus as an epithelial organ assign to the gland an active role in thyrotoxicosis. For some, the thymus in the production of thyrotoxicosis, is a primary factor; for others it is a secondary one. The first group bases its views upon the fact that the mediastinal and cervical lymph nodes are frequently involved and that there is often a concomitant hyperplasia of the lymphatic system, tonsils, adenoids and lymphoid apparatus of the intestines. This hypertrophy of the lymphoid apparatus may be generalized to the whole system, but may involve some lymph organs more than others. The fact that foci of lymphoid cells are frequently found in thyrotoxic goiters is another argument advanced for the lymphoid theory. In short, the whole syndrome is that of status thymolymphaticus. For these no direct relation is seen between the two conditions, thymic hyperplasia and thyrotoxicosis. Fischl and Escherich, however, would not admit such views and claimed that they are theoretical and based upon preconceived ideas. Hedinger claims that hyperplasia of the thymus and status lymphaticus are two entirely different conditions. Matti makes the same claim, basing his conception upon

findings showing that in status thymolymphaticus the medullary portion of the adrenals is not involved, whereas, in status thymicus it is considerably modified. Matti's findings, however, have not been confirmed.

Von Hanseemann, an anatomist, approaching the question from an anatomical point of view, thinks that thymus hyperplasia is secondary to thyroid disturbance. He claims that ordinarily not only the thymus is found hyperplastic but the entire regional lymphatic system also, as the cervical and mediastinal lymph nodes. In his judgment, the thyroid secretion, being pathological, irritates the thymus and the cervical and mediastinal lymphoid systems. In order to substantiate such a theory one should first demonstrate that in such cases the thyroid secretion is pathological, and furthermore, that it shows predilection, if any, for the lymphatic system and thymus. Certainly, thus far the experimental physiology concerning the function of the organ has taught us very little. As we have said before, most of the experiments contradict one another so that, for the time being, one is not warranted in accepting all the results of these experiments as final; we must wait for further confirmation as to their real value. Even the fact that Matti and MacLennan have observed after thymectomy histological changes in thyroids resembling those seen in thyrotoxic goiters needs confirmation.

Hart for a time considered thymic hyperplasia as a primary factor in thyrotoxicosis and thyroid hyperplasia as a secondary phenomenon due to thymic disturbances. Tachycardia, in his judgment, is due to thymic intoxication. In support of this theory, Bircher's and Crotti's experiments might be recalled. We remember that, after transplanting hyperplastic thymus in the epiploon of dogs, Bircher observed that twenty-four hours later they showed marked nervousness, anorexia and thirst. The fourth day exophthalmos appeared which increased until the twentieth day and lasted four or five months. The Graefe symptom was present and tachycardia lasted three months which during the third month went up to 180. Alimentary glycosuria was present as well as lymphocytosis and tremor. Finally, four or five weeks later a goiter appeared, which persisted. Crotti obtained somewhat similar results. On the other hand, Gebele was unable to reproduce Bircher's and Crotti's experiments. In Hart's judgment, thymic intoxication causes tachycardia and hyperplasia of the thyroid in order to neutralize the thymic toxins. As soon as thyroid hyperplasia has reached a certain stage, beyond which neutralization of the toxins no longer takes place, then thyrotoxicosis becomes clinically present.

This theory does not entirely stand the test of analysis. We find many cases of thyrotoxicosis where there is no thymus at all; furthermore, we often find a very large thymus with simple non-toxic goiter. Finally, we sometimes find a hyperplastic thymus in conditions where



there is no goiter and no thyrotoxicosis. On the other hand, how are we to explain the good results obtained in some cases with thymic organotherapy?

It must be said, however, that of late Hart modified his point of view and no longer considered the thymus as the sole cause of thyrotoxicosis. He declared thymic hyperplasia one of the manifestations of an abnormal constitution predisposed to thyrotoxicosis, and to other diseases, as Addison's disease, etc., and that the thyroid disturbances are not the direct result of thymic disturbances. In his judgment the thymus is still the primary cause of tachycardia and of the postoperative delirium cordis. Needless is it to say that Hart's conclusions are purely theoretical.

Ghierka, Rössle and Gebele admitted that there is a vicarious function between the thyroid and the thymus; that hyperplasia is only a manifestation necessitated by the increased function, and when the thyroid becomes functionally insufficient that the thymus tries to meet the deficiency. Gebele based his point of view especially upon experiments where three to nine weeks after implantation of the thymus he was able to perform a total thyroidectomy without observing tetany. Of course, these experiments are not conclusive. They confuse the issue between thyroid, thymus and parathyroids.

Sajous thinks the thymus is not an organ of internal secretion. He considers that "The function of the thymus is to supply through the agencies of the lymphocytes the excess of nucleins in the body, particularly the osseous, the nervous, and the genital systems during infancy, childhood, and even later life. It may be to construct the nuclei of these cells." On account of this richness in nucleins he thinks the thymus takes part in the oxidation and autoprotective processes of the body, and that one of its main functions is to metabolize the phosphorus. Conclusive evidence, however, for this theory is still lacking.

So far, the microscope has been unable to throw much light upon the problem. *The histological structure of the thymus in hyperthyroidism* is exceedingly variable and of difficult interpretation. This is largely due to the uncertainty which still exists about the normal histology of the gland. Schridde, however, observed a marked hyperplasia of the medullary substance characterized by an increase in volume and in the size of the medullary cells; by the great volume of Hassal's corpuscles containing foci of fatty degeneration, and by the hypoplasia of the cortical substance. Cappelle and Bayer found the same lesions, except that the cortical substance instead of being atrophied is hyperplastic.

Crotti made the following observations: In some cases he found a marked hyperplasia of the medullary substance and a concomitant hypoplasia of the cortical portion. The reticular cells in the medullary substance were numerous, hyperplastic, while Hassal's corpuscles were

rather diminished in number and showed signs of hyaline and calcareous degeneration. In other cases there was hyperplasia of the cortical and of the medullary substances. The reticular cells in the medullary portion contained a great many hyperplastic reticular cells and enlarged Hassal's corpuscles, showing all degrees of degeneration. The cortical portion contained a reticulum and, of course, a great many thymic cells. In both forms the eosinophile cells seemed to be quite prevalent.

From all that has been said one should not conclude that thymus hyperplasia has no bearing upon thyrotoxicosis, and that its presence is not to be considered as a symptom of ill omen. Cappelle and Bayer, in 1911, reported a case operated by Garré of a young woman with marked thyrotoxic symptoms, namely, tremor, exophthalmos, dilatation of the heart, palpitation, tachycardia, pulse 140, leukopenia, and 39.3 per cent leukocytes. At the same time there was a moderate enlargement of the cervical sympathetic lymphatic system. The x-ray showed a shadow suggestive of thymus. Thymectomy was performed, 15 grams were removed and the patient became much better. The pulse-rate went down to 100; the lymphocytosis of the blood disappeared entirely and the patient gained in weight. Five months later, however, the thyroid became enlarged again but did not show any vascular symptoms. Lymphocytosis reappeared; the patient became much worse again, and a unilateral thyroidectomy was performed, after which the patient got relief. This only shows that thyroidectomy ought to have been performed at the same time the patient underwent thymectomy. Furthermore, unilateral resection of the thyroid is insufficient. It was a bilateral resection that should have been done.

Schumacher and Roth, in 1912, performed thymectomy, removing 49 grams of thymus in a patient afflicted with goiter, with thyrotoxic symptoms, exophthalmos, and symptoms of muscular myasthenia. The patient was greatly benefited but later on the goiter became very large and thyroidectomy had to be performed. In the meantime the pulse which was 140 came down to the neighborhood of 80. Lymphocytosis disappeared and the general condition of the patient was good. The thyroidectomy was performed mostly on account of the mechanical symptoms.

Von Haberer, in 1913, reported another very interesting case: The patient was a man suffering from the most intense hyperthyroidism accompanied by marked choking spells. Ligation and thyroidectomy were performed by eminent surgeons, one of them none other than Kocher. Yet, the improvement of the patient was only slight and temporary, so that he soon fell back into a pitiful condition which was considered hopeless. Beside the thyrotoxic symptoms the dyspnea was intense and the condition of the heart so bad that death was expected

at any time. Von Haberer decided to attempt the removal of the thymus, but at the operation was much disappointed to find no apparent trace of thymus. All that he was able to remove was a small piece of fat, which, nevertheless, proved under microscopical examination to contain some thymus gland. From the time of this operation the improvement of the patient was so marvelous that he recovered rapidly and entirely.

Cappelle and Bayer, in 1913, reported another interesting case, that of a young woman, twenty-seven years old, who had previously undergone a pelvic operation, shortening of the round ligaments. Later on the patient developed thyrotoxicosis characterized by palpitation, tachycardia, exophthalmos, tremor, diarrhea and vomiting, and loss of flesh and loss of hair. No goiter was to be seen, but a slight hyperplasia could be felt. Lymphocytes were 46 per cent and eosinophiles were 5.5 per cent. Thymectomy was performed, 15 grams of the gland being removed. The patient stood the operation very well and six months after was entirely cured.

That the thymus plays an important part in Graves's disease, in Halsted's judgment, has been demonstrated beyond all question by the results which have followed thymectomy. Halsted, in 1914, reported 500 cases, 60 per cent of which were approximately cured, and 25 per cent showed slight improvement.

From all that has been said so far, it is apparent that a direct relation between the thyroid and the thymus in thyrotoxicosis cannot be denied.

**What is This Relation?**—In order to answer the question, Falta, Eppinger and Hesse, by using the stimulating action of adrenalin upon the sympathetic, and the stimulating effect of pilocarpine and the depressing effect of atropine upon the vagal system, tried to study what relation exists between the sympathetic and the autonomic nervous systems. On the strength of their experiments, Eppinger and Hesse came to the conclusion that some of the symptoms seen in thyrotoxicosis are dependent upon sympathetic disturbances and some others upon disturbances of the autonomous system. In the sympatheticotonic cases the thyroid is mostly responsible, whereas in the vagotonic cases the thymus is mostly at fault. According to A. Kocher, this difference exists, likewise, in the histological picture of the gland. Basing his opinion upon the examination of 200 thyroids, he claims that in the sympatheticotonic cases there is a marked proliferation of the large cells; they are highly cylindrical, and bulge into the alveoli, which contain little or no colloid. If, however, there is a marked proliferation of the small and polymorphic cells, then we have a mixture of sympatheticotonia and vagotonia. If both conditions are found markedly developed then the case is a severe one. Cappelle and Bayer reported the same findings.

Falta, Eppinger and Reutinger have tried to show that thyroid



extract has at the same time a sympatheticotrope and a vagotrope influence; that the sympatheticotrope effect is stronger than the vagotrope and that it has a depressing effect upon the pancreas, which is in itself vagotrope. Kostlivy, in 1910, basing his conclusions upon the blood examination and epinephrin content of the blood before and after thyroidectomy, claimed that the exaggeration of the thyrotoxic symptoms seen after thyroidectomy is due to the fact that operation removed certain vagotrope portions of the glands, hence causing destruction of the equilibrium between the two systems, the sympathetic taking the upper hand.

Svehla asserted that the thymus gives off an internal secretion and thinks thymic death is due to this substance acting on the heart and nervous system. By injecting an aqueous solution into animals, Svehla found a diminution in the blood-pressure and increased rapidity of the pulse. Repeated injections caused the death of the animals; therefore Svehla considers the "*mors thymica*" as a consequence of hyperthymization resulting in a diminution of the blood-pressure. These experiments, however, do not mean a great deal, inasmuch as Swale Vincent and others have shown that organic extracts of most organs will cause a lowering of blood-pressure.

It has been said that lymphocytosis is dependent upon thymic hyperplasia. Some of the observations above mentioned would seem to show indeed that after thymectomy the lymphocytosis disappears entirely and rapidly. Furthermore, the fact that after thyroidectomy, even when the patient is cured, lymphocytosis remains for a long time, might be interpreted as showing that lymphocytosis is dependent upon thymic hyperplasia. This view is strengthened by the fact that Klose, Lampe and Liesegang have observed lymphocytosis in 60 per cent of the cases of thymic hyperplasia in children and that after partial thymectomy this lymphocytosis went down to 37 per cent.

A very interesting case is the one reported by Cappelle and Bayer, who gave thymus extract to a patient who had been cured of thyrotoxicosis by thymectomy. At once, sweating, palpitation and eosinophilia appeared. That, however, lymphocytosis is purely due to thymic hyperplasia cannot be ascertained nor maintained, because too many cases have been observed where lymphocytosis appeared after thyroid extract feeding. Furthermore, time and time again, after thyroidectomy alone, lymphocytosis has been known to disappear entirely just as after thymectomy.

So far as I am personally concerned, I can but believe, until shown otherwise, that there is a direct etiological relation between thyrotoxicosis and hyperplastic thymus. In the great majority of cases hyperplasia of the thymus is secondary to thyrotoxicosis. The thymus being a



lympho-epithelial organ reaches toward the thyrotoxic goiter, which is simply a toxic thyroiditis in two ways:

1. By hyperplasia of its lymphoid portion, accompanied or not by hyperplasia of the cervical and mediastinal lymph nodes.
2. By hyperfunction of its epithelial constituents.

### HYPERTHYMISM.

Already in 1908, Hart came to the conclusion that beside a *thyroid Basedow* there could be such a thing as a *thymus Basedow*, the latter form being characterized by the same cardinal symptoms as those seen in thyroid Basedow. This view has been held by Capelle, Bayer, Bircher and Klose.

**Thymogene Basedow.**—Indeed, as in the cases reported above, inasmuch as they activate each other, there appears to be unquestionably a synergic action between the thyroid and the thymus. This seems to be demonstrated experimentally, as well as by cases of Basedow's disease where surgical interference on the thyroid did not give the expected results, but where the cure was secured most rapidly and most completely by adding to it the removal of the thymus. We may say, furthermore, that the majority of cases of Graves's disease are of thyroid origin, but that their intensity may be increased by a concomitant thymic hyperplasia. In other words the deleterious effects of the two glands are mutually increased; consequently, the presence of the thymic hyperplasia must always be looked for, and must always be regarded as a complication. We may furthermore admit that we may have some cases of Graves's disease of purely thyroid origin. Finally, we may have both forms combined.

In borderline cases of hyperthymism, we find the following syndrome of asthenia, loss of weight or strength, of varying degrees of labile pulse, tachycardia, perspiration, tremor, sometimes depression, and often slight elevation of temperature without any special course of pathological findings in the thyroid gland and without ocular symptoms. The diagnosis in these instances lies largely between moderate thyrotoxicosis, incipient tuberculosis, psychoasthenia, psychoneurosis, neurasthenia, and underlying nervous states. In most of these cases the usual medical treatment does not bring any great relief. In many instances the epinephrin test is positive and a number of these cases submitted to operation show no marked improvement.

**Differential Diagnosis between Thymic and Thyroid Basedow.** If all these conditions are true, it will then be necessary to ascribe to every case of Graves's disease its true origin. In other words, we shall

have to decide if we have to deal with a thyroid, or a thymic Basedow, or a mixed one. Let it be said right now that in the greatest number of

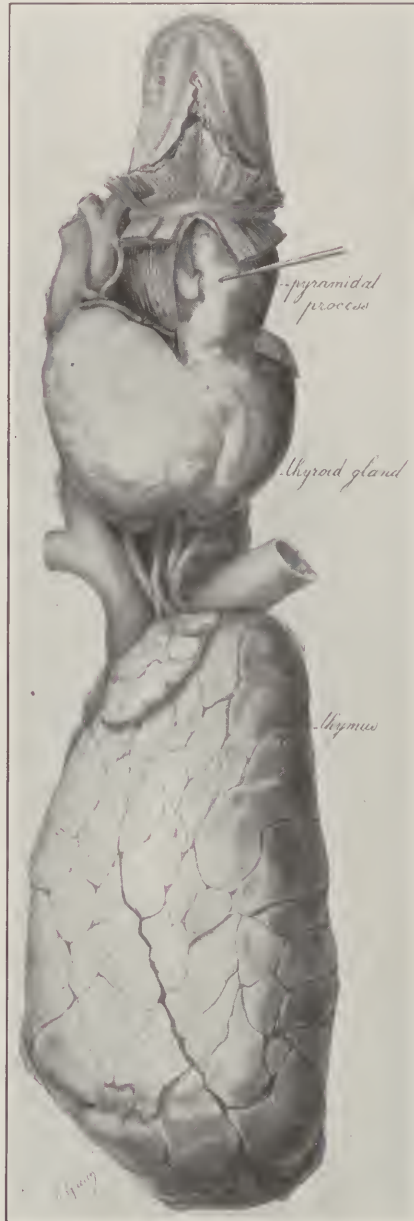
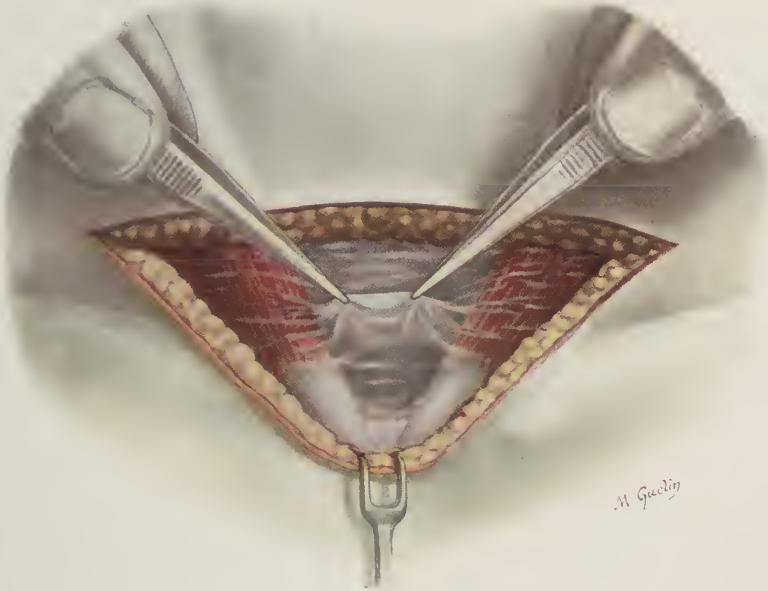


FIG. 104.—Thymic hyperplasia and Basedow's disease, a postmortem specimen. Note that the thymus covers the heart entirely.

cases we shall have to deal with a thyroid Basedow. This form, however, may be combined with the thymic Basedow. The pure form of thymic Basedow is rare.

# PLATE XXXVII

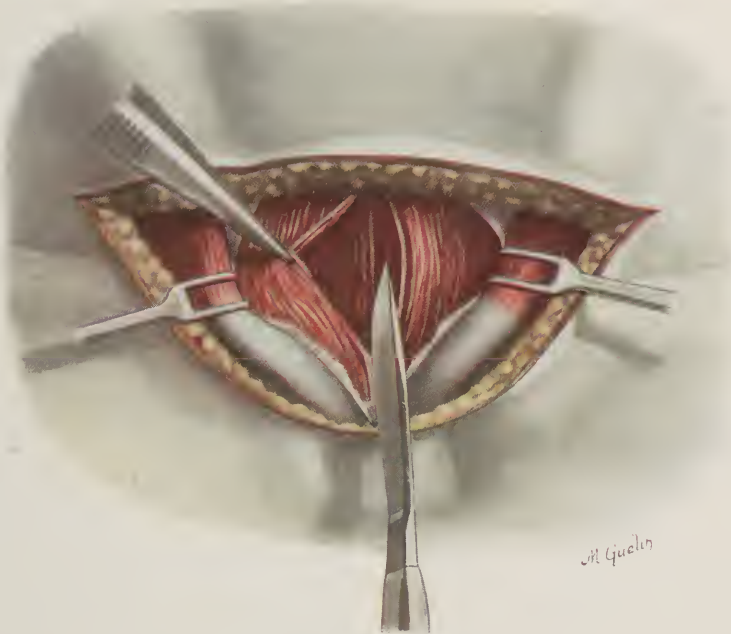
FIG. 1



Thymectomy.

The two flaps obtained after the transverse incision has been made are retracted and the superficial cervical fascia is grasped between two forceps and cut in the middle line.

FIG. 2



Thymectomy.

The prethyroid muscles are divided in the middle line and retracted laterally.





How are we going to differentiate these two forms? As was seen in the chapter on Basedow's disease, in many cases there is a certain group of symptoms which seem to be more dependent upon the excitation of one of the two nerves of vegetative life, the *vagus* and the *sympathetic*. If the predominating symptoms are of vagus origin the case is called *vagotonic*. If, on the other hand, the predominating symptoms are of sympathetic origin, the case is called *sympatheticotonic*. We have seen, too, that according to Eppinger and Hesse, the vagotonic symptoms are:

1. A moderate degree only of tachycardia, but intensely marked subjective symptoms.
2. A marked Graefe symptom with pronounced enlargement of the eyelids, accompanied, however, by a moderate exophthalmos, but with no Moebius; the lacrymal secretion is increased.
3. Profuse perspiration.
4. Diarrhea, hyperacidity, vomiting.
5. Increased eosinophilia.
6. Alimentary glycosuria.

According to the same authors the sympatheticotonic symptoms are:

1. A marked exophthalmos but no Graefe; with positive Moebius, and with suppressed or diminished secretion.
2. Pronounced tachycardia, however, with only moderate subjective symptoms.
3. No perspiration, no diarrhea, no vomiting.
4. Marked falling of the hair.
5. Eosinophilia, no alimentary glycosuria.
6. Occasionally a slight increase in temperature.

According to Eppinger and Hesse the vagotonic symptoms are produced by a thymic hormone which would act as an excitant of the vagal system. It is not, however, demonstrated beyond all doubt that all the symptoms considered as vagotonic are really of such origin. The same is true of sympatheticotonic symptoms. There will be needed further work in order to throw light upon this subject.

So far the true thymogene Basedow is still difficult to diagnose beforehand. As a rule, this diagnosis is made only retrospectively after the thyroid has been removed, after it is found that the microscopical examination does not show the typical microscopical changes in the thyroid, known as *pathognomonic* of the disease, and after one sees that the clinical results do not come up to the expectation. Only then the suspicion of a thymic Basedow dawns upon one's mind. In my own experience the *x*-rays as a diagnostic means in adults have not proved as useful as I thought they would. In a series of several hundred goiters of all kinds, I systematically made roentgen examinations. In many instances I was able to demonstrate beforehand the presence of an

enlarged thymus, but in others in which, according to the radiogram, no thymus was present, I was much surprised to find at the time of operation quite an important thymic enlargement. A symptom which I think is of good diagnostic value in diagnosing thymic hyperplasia complicating a Basedow case, is marked *muscular asthenia*. Furthermore, the presence of small lymph nodes in the cervical region must be regarded, in my judgment, as a strong presumption in favor of the presence of thymic hyperplasia; in fact they belong to the status thymolymphaticus.

In conclusion one may say that a high lymphocytosis with moderate enlargement of the thyroid; a moderate tachycardia, but with intense subjective symptoms; gastro-intestinal symptoms; the presence of small cervical lymph nodes; an increased area of dulness over the manubrium sterni; a prolonged expiration over this area of a character which is truly tubular; all these symptoms together with a positive x-ray are strongly suspicious of a thymic hyperplasia.

#### **Treatment of Thymic Hyperplasia Complicating Graves's Disease.**

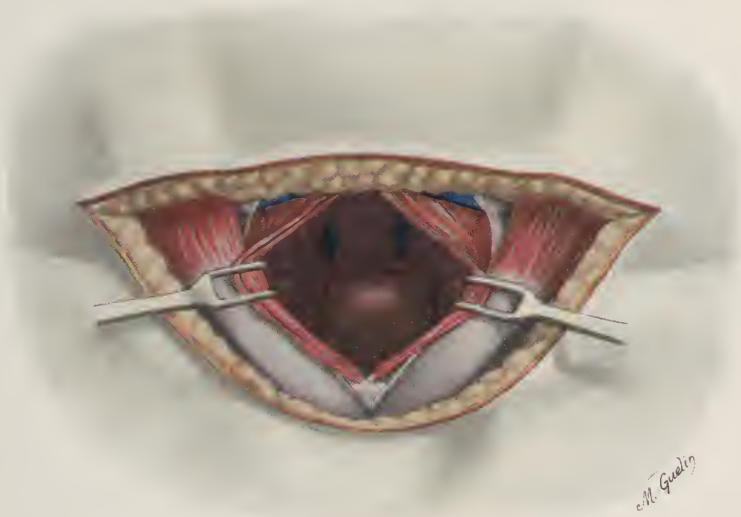
—From what has been stated, it follows that thymic hyperplasia in goiter surgery can no longer be disregarded. It is a serious complication which occurs not only in Graves's disease, but in simple goiter also. It is likely to kill the patient either by choking him or by causing a thymic intoxication leading to hyperthymism and possibly to acidosis. What shall we do then? Simply remove the thymus. Simply combine *thymectomy* with *thyroidectomy*. And that is precisely what I have been doing in every goiter case that has come my way. In every case as soon as thyroidectomy is terminated, I explore systematically the upper anterior mediastinum, and whenever a thymus is found it is removed. Of course, the thymectomy can be only partial. In so doing, not only the remote results are better, but the operative course is also far more satisfactory. First of all, the possibility of a mechanical thymic death is eliminated, and this certainly is a great relief. Always before this, after thyroidectomy, I felt uneasy and anxious for twenty-four hours, because I feared that a choking spell of thymic origin might occur. There are no longer such fears.

Furthermore, the postoperative reaction which so often follows an operation for goiter, but especially the thyrotoxic type, is unmistakably better; temperature is not so high; nervousness is not so extreme; delirium is far less marked; acidosis is less severe, and what is more the death-rate is certainly less. All told, I consider this combined operation a great step forward in the surgical treatment of Graves's disease.

**Treatment of Thymic Hyperplasia in Children.**—In cases of thymic hyperplasia in children if the mechanical symptoms are alarming I operate at once. What is the use of running the risk of losing the little patient by trying any other method of treatment when the operative

# PLATE XXXVIII

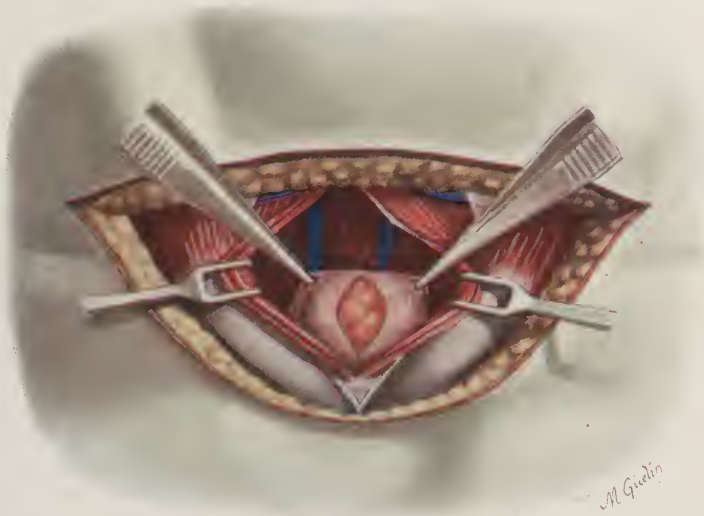
FIG. 1



## Thymectomy.

After the sternohyoid and the sternothyroid muscles have been separated in the middle line and retracted, a more or less round mass is often seen bulging upward with each expiration and disappearing again with each inspiration. That is the thymus.

FIG. 2



## Thymectomy.

If the thymus is grasped between two forceps and its capsule cut, the thymic parenchyma bulges out as if under pressure, especially with each expiration.





treatment is still safe? Two of my cases which had a marked thymus hyperplasia and in which the thymus compressed not only the trachea, but also the esophagus, gained an ounce the same day that thymectomy was performed and continued to do so for two weeks after. In three months the two little patients had become prosperous and healthy. Several others who had choking spells increasing constantly in intensity, so much so that when brought for operation, they were between life and death, as soon as thymectomy was performed, soon breathed regularly and regained perfect health.

If, however, operation cannot be performed because of impending death, intratracheal rubber tubes should be introduced either through the larynx or through a tracheotomy opening. It is important to make sure that the tube opens at the end and not on the side. It is important, too, to extend the tube well into the trachea so as to pass the point of compression. We must remember, however, that tracheotomy ought to be resorted to only as a last measure, because we know by experience that tracheotomy combined with thymectomy is usually fatal on account of postoperative bronchial pneumonia, and especially mediastinitis.

If the choking spells are not alarming, *x*-ray treatment is the method of choice.

**Operative Accidents.**—The only accident observed in some cases is a subcutaneous emphysema taking place during the operation and localized in the upper anterior part of the thorax as well as in the lower part of the neck. It disappears a few hours after the operation. It betrays its presence by a fine crackling upon pressure with the finger, similar to the one observed in compressing newly fallen snow, and must be due to some minor injury of the apex of the lung.

## CHAPTER LII.

### SURGICAL TECHNIC OF THYMECTOMY.

**Anesthesia.**—In adults it is self-evident that almost invariably thymectomy should be performed under anesthesia. In children, especially in newborn, the dyspnea may be so intense that anesthesia, no matter what form, may only increase the dyspnea, consequently, in such conditions the operation may have to be performed under local anesthesia or without any anesthesia at all, as in a newborn, for instance. In the great majority of cases, however, a complete anesthesia is necessary, as the crying from pain will only serve to increase the congestion

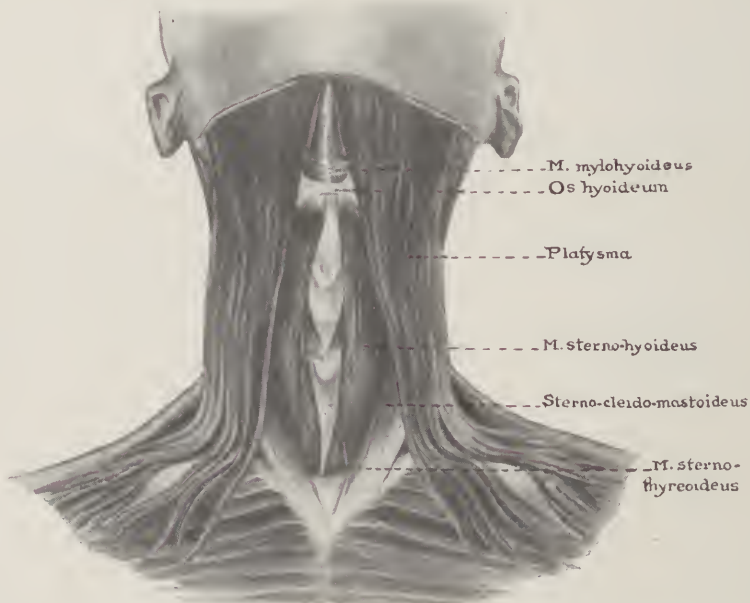


FIG. 105.—Anatomy of the muscles involved in performing thymectomy.

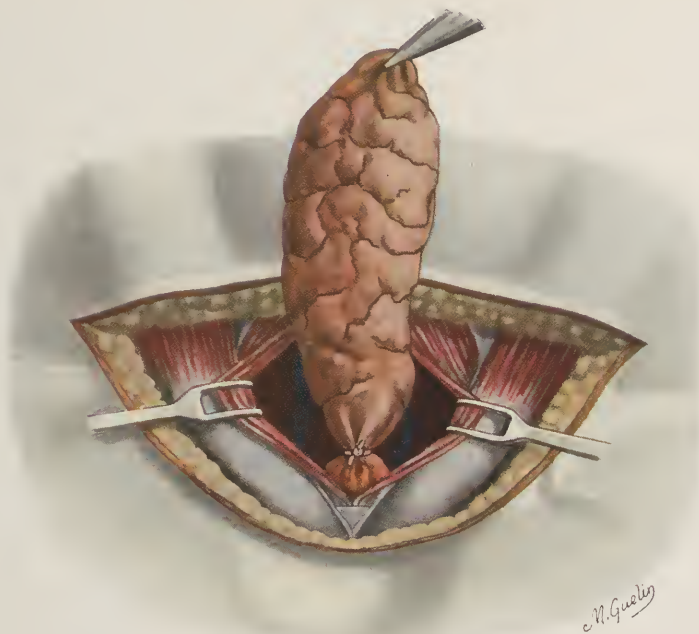
of the thymus and accentuate the dyspnea. In small children chloroform seems to be preferable to ether.

**Surgical Technic.**—1. A short, transverse incision is made just above the manubrium sterni. The skin is cut and the two flaps are resected, one upward and the other downward.

2. The superficial cervical fascia is clamped between two forceps and cut in the middle line. (Plate XXXVII, Fig. 1.)

## PLATE XXXIX

FIG. 1



### Thymectomy.

When isolated, the thymus is ligated snugly at its basis in order to catch the few thymic vessels and it is cut far enough so as to prevent the ligature from slipping, thus causing a hemorrhage almost impossible to check except by packing.

FIG. 2



### Thymectomy.

The prethyroid vessels are then sewed together in the middle line, subcutaneous tissue is sutured by itself and intradermic suture is performed.





3. The prethyroid muscles are separated in the middle line and retracted laterally. (Plate XXXVII, Fig. 2.)

4. After the sternohyoid and the sternothyroid muscles have been separated in the middle line and retracted, one sees a more or less round mass bulging upward with each expiration and disappearing again with each inspiration. *This is the thymus.* (Plate XXXVIII, Fig. 1.) In children, and sometimes in adults, the hyperplastic thymus reaches the lower pole of the thyroid, so that it is easily discovered.

5. The thymus is then clamped between two hemostats and pulled gradually upward. Great care should be taken to clamp every bit of loose tissue around the capsule of the thymus so as to catch every small vessel.

The *extracapsular method is the method of choice*, as usually the thymus is easily loosened from the surrounding structures. When, however, there is perithymitis causing some difficulty in getting the thymus up, it is better then to perform an *intracapsular thymectomy* as shown in Plate XXXVIII, Fig. 2. The glandular capsule of the thymus is then opened, and as soon as this is done the thymic parenchyma bulges out as if under pressure, especially with each expiration. The parenchyma is then shelled out slowly, gradually and more or less easily. As said before, however, at least in my experience, the extracapsular method is the one of choice, provided one is careful to clamp every particle of loose connective tissue in connection with the thymus. In the numerous thymectomies which I have performed, I have never met with an unpleasant hemorrhage following this mode of operating.

6. When sufficiently isolated, the thymus is then ligated snugly at its base (Plate XXXIX, Fig. 1) in order to catch the few thymic vessels which supply the gland; a little bit of tissue is left outside of the ligature in order to prevent it from slipping. If this should happen a hemorrhage sometimes difficult to check, except by packing, will occur.

7. After all ligations of the clamped vessels have been performed, the prethyroid muscles are sewed up again in the middle line by running suture or by one or two interrupted stitches. (Plate XXXIX.) The subcutaneous tissue and platysma are sewed up by continuous running suture. The operation is concluded with an intradermic suture.



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